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Editorial

Oesophageal echocardiography

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The image quality of standard precordial echocardiograms can be unsatisfactory for various reasons. These include chronic pulmonary disease, obesity, chest deformities, and changes in the chest wall with age. In such patients important diagnostic information can more readily be obtained by oesophageal echocardiography.¹ Furthermore, even in patients with apparently excellent precordial imaging the oesophageal approach improves the signal to noise ratio because it circumvents the chest wall. This permits both better detection of poorly echo reflective structures such as thrombi and allows the use of higher frequency transducers, which give more detailed imaging of cardiac structure. In addition, some structures that are poorly displayed by the standard precordial approach are better visualised by the oesophageal approach. These include large areas of the atrial cavities, the left main coronary artery (and its proximal branches), and the thoracic aorta.²⁻⁴

Intraoperative applications

This new approach gives useful new information in several clinical situations and cardiac conditions. For example, in patients at high risk of cardiovascular complications the oesophageal probe can be used to monitor left ventricular function during anaesthesia without interfering with the surgical procedure.^{5,6}

Oesophageal monitoring of left ventricular wall motion during operation permits the early detection of ischaemia and intervention to prevent myocardial infarction.⁷⁻⁹ Oesophageal echocardiography was a more accurate predictor of changes in left ventricular filling than flow directed wedge catheters⁷ (currently

the accepted intraoperative technique for monitoring of left ventricular function). The immediate effects of coronary revascularisation can be studied by oesophageal echocardiography¹⁰ and the technique can be used to monitor intracardiac air and other emboli passing through the heart.¹¹⁻¹⁴ The method opens a new area of research into the cardiovascular effects of anaesthetic drugs and interventions.^{15,16} As with gastrointestinal endoscopy there is a risk of oesophageal perforation. Over three thousand cardiac studies have now been reported with no episode of perforation. The introduction of transducers without optical fibres seems to be as safe as the introduction of transducers with optical fibres. We believe that oesophageal echocardiography is safe when carried out by cardiologists and anaesthetists who are trained in the introduction of gastroscopes. Although the technique is valuable for intraoperative monitoring, oesophageal echocardiography will perhaps have its greatest impact when applied to intraoperative diagnosis. Oesophageal imaging combined with colour flow studies may be able to give the surgeon an intraoperative angiographic assessment of any surgical repair or valve replacement that lies in a plane accessible to the echo beam.¹⁷ With modern cardioplegia, bypass time is no longer a limiting factor in surgical repair. Such immediate intraoperative evaluation of the repair should permit more precise and effective operations because bypass can be extended for further surgery if imaging shows that this is necessary.

Emergency and outpatient applications

Oesophageal echocardiography can also be used to assess the critically ill patient in whom an underlying acute cardiac event is suspected.¹⁸ This technique is especially suitable for ventilated patients in the emergency room or in the intensive care unit when precordial echocardiography does not give sufficient

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information and in whom other diagnostic methods are not applicable.

It is likely that transoesophageal echocardiography will find an important place in the outpatient assessment of patients with suspected cardiac disease.

Before oesophageal echocardiography the patient must fast for about four hours. Usually patients do not need premedication if they are given a full explanation of both the reason for the study and the procedure. But some may need standard endoscopy premedication. Lignocaine (10%) is sprayed on to the hypopharynx and patients are studied in the left lateral decubitus position. The gastroscope is introduced in the standard manner with or without fiberoptic imaging. Rotation and angulation of the gastroscope give different views of the heart. The probe must be advanced to the fundus of the stomach to record all the available cross sectional views of the heart. Most of the clinically useful information is usually obtained within ten minutes. An experienced operator will obtain images of high quality in almost all patients. Relative contraindications to oesophageal echocardiography are difficulty with swallowing, a history of oesophageal disease, and pre-existing radiation treatment. If these features are present a gastroenterologist should be consulted about the feasibility of the examination.

Oesophageal imaging gives fewer section planes than the precordial approach. But in the structurally normal heart it gives excellent visualisation of the left atrium, mitral valve, and left ventricular outflow tract. The aortic valve can only be visualised in an oblique section. The aortic root and left main coronary artery and its proximal branches are also well displayed. The technique is rapidly being adopted as the investigation of choice for aortic dissection because it gives good images of the descending thoracic aorta.^{4,19,20} Aortic dissection can be diagnosed within 10 minutes of clinical suspicion. The mortality rate in type I aortic dissection is approximately 5% in the first hour. Computed tomography takes longer than oesophageal echocardiography and in our experience earlier emergency surgery may reduce overall mortality in this group of patients. Patients with chest trauma and acute aortic injury may also benefit from oesophageal echocardiography.

Image quality

Wall motion abnormalities in the proximal and mid ventricular walls are well defined, but the apex of the left ventricle remains a relatively uncharted area. The right heart is not well imaged but may be clearly seen in patients with cardiac rotation or right heart dilatation or both. The interatrial septum and right

atrial appendage are consistently imaged as are the superior and inferior caval veins. The right ventricular outflow tract is not visualised in the normal heart and the pulmonary valve is seen only infrequently. The main pulmonary artery distal to the valve and its bifurcation into left and right pulmonary arteries is seen in over 50% of patients. Ultimately, these relatively poorly visualised areas may become accessible to more flexible and better steered transducers.

Because some areas are particularly well visualised from the oesophagus, the technique is most informative about abnormalities of the aorto mitral valve,^{4,21} left atrium (including appendage thrombi),^{2,4,22} interatrial septum,²³ left ventricular outflow tract, aortic root, and proximal left coronary artery and in the assessment of function of the proximal/mid portions of the ventricular myocardium. In combination with colour flow mapping techniques, oesophageal echocardiography is more sensitive than the precordial approach for detecting regurgitant jets in the left atrium in patients with both acquired mitral valve disease and valve prostheses. Investigation of mitral regurgitant jets by the precordial approach is limited by both the decline in the amplitude of Doppler signals over distance and the poor sound penetration to the area of interest. "Flow masking" behind the mechanical prosthesis is very common²⁴ and reduces the usefulness of assessment of mitral prosthetic regurgitation by the precordial approach. This is not a problem with oesophageal echocardiography because the transducer is placed immediately behind the left atrium.

At present, the transducers that are used for oesophageal echocardiography are too large for neonates or infants. But they can be used in older children and adolescents. We believe that oesophageal echocardiography will give additional information in the assessment of complex atrioventricular connections, Fontan circulation, the success of atrial baffle operation, and complex pulmonary atresia.

Conclusion

Oesophageal echocardiography is a logical extension of standard precordial echocardiography and is a major advance in the care of patients with cardiovascular disease. It provides diagnostic information essential for clinical decision making in patients with inadequate precordial studies. Its superior image resolution and increased sensitivity allow cardiac structure and function to be visualised in great detail. The method has proved to be a valuable means of intraoperative and perioperative monitoring of left ventricular performance in high risk patients and promises to be invaluable in critically ill patients. It

will undoubtedly become the principal method for analysis of both acute and chronic disease of the thoracic aorta, which cannot be seen from the precordial windows. In addition, oesophageal echocardiography is a major diagnostic advance in the evaluation of patients with suspected intracardiac emboli and dysfunction of a mitral valve prosthesis.

We believe that at present oesophageal studies should be performed only by cardiologists at centres with an extensive experience of the application of all routine diagnostic modes of cardiac ultrasound and an experienced gastroenterological department. Cardiologists intending to use oesophageal echocardiography must be trained by an experienced gastroenterologist.

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The ST segment of the ambulatory electrocardiogram in a normal population

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SUMMARY The behaviour of the ST segment in everyday life was studied by ambulatory electrocardiography in 111 normal volunteers. Fifteen were excluded because of abnormal exercise responses (10 subjects) and significant postural ST segment shifts (five subjects). This left 62 men and 34 women, mean (SD) age 40.5 (12.6) years (range 20-67 years). Ambulatory monitoring of leads CM5 and CC5 for 24 hours was followed by a maximal treadmill exercise test. The tapes of the ambulatory monitoring were analysed by a computer aided system. The computer printed trend plots of the ST segment (measured both at the J point and at J + 60 ms) to detect episodes of ST segment elevation and depression, which were confirmed by visual analysis of real time print-outs. Twelve subjects showed "ischaemic" ST segment depression and nine subjects showed ST segment elevation. Eight people with ambulatory ST segment changes were studied during exercise by radionuclide ventriculography and thallium-201 imaging scans. Although seven of the eight thallium studies were normal, radionuclide ventriculography showed functional impairment in five cases. Seven of the 10 subjects with abnormal exercise tests were similarly investigated and their results followed the same pattern, with normal thallium images in six and functional impairment in four. Ambulatory electrocardiography was repeated in 20 people after a median of 20 days. The ST segment changes were reproducible.

ST segment changes of an apparently ischaemic nature occur even in a carefully defined normal population but they do not necessarily represent latent clinically significant coronary artery disease. This indicates that ST segment changes seen in patients with known obstructive coronary artery disease should be interpreted with caution.

Horizontal and downsloping depression of the ST segment of the electrocardiogram is a well established marker of myocardial ischaemia¹ that may or may not be accompanied by angina.²⁻⁵ A wide variety of physiological events^{6,7} and drugs can, however, produce ST segment changes identical to those interpreted as indicating myocardial ischaemia.

Ambulatory monitoring of the electrocardiogram for periods of ST segment depression has been widely used for the detection and quantification of ischaemia.³⁻⁵ Some direct recording systems produce low frequency phase distortion, however, which mimics ischaemic ST depression⁸ and the criteria

used to assess the magnitude and duration of ischaemic ST change remain empirical.

The results of previous studies on "normal" populations were contradictory. Possible reasons for this include biased selection of subjects,^{9,10} lack of physical screening,⁹ and failure to exclude "vaso-regulatory" and postural ST segment changes.^{10,11}

We studied ambulatory ST segment deviation in a carefully selected normal population to define the variety, duration, and repeatability of ST segment deviation during 24 hours of normal activity.

Patients and methods

We selected 116 people from the local population by taking every tenth record card from the index files of three local general practices. We excluded cards indicating any history or symptoms suggestive of

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cardiovascular disease. Informed written consent was obtained from all volunteers, and the project was approved by the hospital ethics committee.

The subjects were screened by physical examination, a 12 lead electrocardiogram, and a questionnaire on their personal and family histories. Five who were taking medication or had a history suggestive of cardiovascular disease were excluded. We studied the remaining 111.

RECORDING OF AMBULATORY TAPES

Orthostatic tests for postural ST segment shifts in the supine, prone, lateral, sitting, and standing positions; the Valsalva manoeuvre; and 60 s of hyperventilation were performed with a Computer-Assisted System for Exercise (Marquette Electronics Inc.) and we obtained a digital recording of the ST shift to the nearest 0.1 mm. All subjects were then fitted with an Oxford Medilog MR 20 frequency modulated recorder with the bipolar leads CM5 (negative electrode at the manubrium and exploring electrode at LV5) and CC5 (negative electrode at RV6 and exploring electrode at LV5). We were careful with skin preparation and electrode placement and fixing. The electrodes were held in place by a close-fitting elastic vest. The subjects were instructed to use the marker button for timing events such as smoking, driving, and other important activities.

Volunteers were monitored for 24 hours during normal daily activities, and then they performed a symptom-limited graded treadmill exercise test with the same leads and a standard protocol.¹² An abnormal response was defined as horizontal or downsloping ST depression of ≥ 1 mm that persisted for at least 80 ms (heart rate $< 105/\text{min}$) or 60 ms (heart rate $> 105/\text{min}$) after the J point. The exercise electrocardiogram leads were simultaneously recorded on the Medilog to enable a retrospective validation of each ambulatory tape.

Twenty volunteers underwent a second 24 hour ambulatory recording with the same equipment after an interval of 1–225 (median 20) days.

ANALYSIS OF AMBULATORY TAPES

All the tapes were analysed by an updated version of a computer system reported from our laboratory⁸ and also visually by two independent observers.

The computer system, which was based on a modified Pathfinder II analyser (Reynolds Medical, UK) and a MINC 11/23 computer (Digital Equipment Corp.), processed both leads simultaneously, measured ST level at the J point and at J+60 or J+80 ms, excluded artefact and extrasystoles, and captured patient event marks. The Pathfinder

analyser generated a superimposed electrocardiographic display with three bright spots, one of which was manually located on the PR segment to identify the isoelectric point. The second spot was positioned at the J point. The third spot was automatically located 60 ms after the J point, or 80 ms if the heart rate fell below 105 beats per minute. The electrocardiogram was continuously scanned which enabled the Pathfinder to flag artefacts and exclude extrasystoles; the operator could also intervene to indicate any artefacts missed by the automatic system. The signals from the Pathfinder were processed by the computer which stored 20 s average values of ST and heart rate on diskette, together with the time, patient event marks, arrhythmia flag, and a marker of artefact detected either automatically or by the operator. The recorded quartz crystal clock ensured accurate timing on each tape.

After we completed the tape scan we retrieved the ST data from the diskette and plotted them as a 24 hour trend together with heart rate, event marks, and an indication of horizontal or downsloping ST segment. Artefact was automatically indicated by lifting of the plotter pen so that misleading data did not appear on the plot. Separate plots were obtained for trends of the J point and of the (J+60 ms) levels to confirm all suspected downsloping ST depression episodes. Where (J+80 ms) values had been stored these were converted to (J+60 ms) values by interpolation.

Two independent observers performed further visual analysis by printing out on paper at 25 mm/s all episodes of significant or nearly significant ST change, both depression and elevation, seen on the trend plots. A significant episode was defined as ≥ 1 mm of horizontal or downsloping ST segment depression persisting for at least 60 ms after the J point and maintained for ≥ 1 minute. Nearly significant episodes were defined as 0.5–1.0 mm of horizontal or downsloping depression maintained for ≥ 1 minute. For the repeatability study a less stringent criterion was used to obtain more episodes. Here a significant episode was defined as ≥ 0.5 mm of ST depression at J+60 ms maintained for ≥ 1 minute. The tapes were also examined for T wave changes; a doubling of the T wave height from the resting value was considered as "peaking". Episodes of T wave flattening and inversion were also assessed.

VALIDATION

For every subject the tape analyser was validated against the Marquette exercise system by simultaneously recording with the same electrodes a two lead exercise electrocardiogram (CM5/CC5) both on the Medilog tape and on the exercise system. The tape analyser was then used to derive values for one

minute average ST and heart rate that were compared with corresponding one minute averages extracted from the Marquette data by a special retrieval program.

RADIONUCLIDE INVESTIGATIONS

We asked volunteers who showed abnormal ST segment depression during ambulatory monitoring or during the exercise test to consent to radionuclide angiography and exercise thallium-201 imaging.

Equilibrium radionuclide angiography was performed at rest and during supine graded ergometric exercise.^{13,14} The blood pool was labelled *in vivo* with stannous pyrophosphate and 740 MBq of technetium-99m. Imaging was carried out with a mobile digital small field of view gammacamera (Elsint) in a modified left anterior oblique view (best septal) with a 10° to 15° caudal tilt. We divided the averaged cardiac cycle into 32 frames per cycle at rest and 24 frames per cycle during exercise to provide a high resolution time-activity curve from which the left ventricular ejection fraction was calculated by a semiautomatic algorithm.¹⁴ We defined failure to increase the ejection fraction by 5% in the presence of abnormal wall motion as an abnormal response to exercise. The peak filling rate was calculated as the slope of a 100 ms segment of the time-activity curve around the point of maximal slope before diastasis.¹³

We performed thallium-201 imaging after a symptom limited exercise test.¹² A physician who was unaware of the results of the other investigations analysed all the radionuclide studies.

STATISTICAL ANALYSIS

Data were expressed as mean (SD). The figures show the standard error of the mean. Analysis of variance was performed for the repeat tapes; for convenience all components of variance were redefined as components of variability by taking the square root.

Results

We studied 72 men and 39 women (aged 20–67 years) (table 1). We excluded five people because they showed more than 0.5 mm ST depression in response to orthostatic testing; a further 10 showed a positive response to exercise testing and we analysed their

data separately (group B, fig 1). The remaining 96 subjects (62 men and 34 women) (aged 45.6 (12.4)) made up group A (fig 1).

SUBGROUP OF SUBJECTS WITH NORMAL EXERCISE RESPONSE (GROUP A, FIG 1)

Validation of ambulatory tapes (table 2)

We obtained clean exercise recordings from 94 of the 96 subjects for both the Marquette exercise system and the Medilog recorder. In 50, the two systems agreed to within 0.5 mm in both leads throughout exercise. Analysis of differences (table 2) showed a mean (SD) discrepancy of 0.09 (0.2) mm on lead CM5 and 0.07 (0.2) mm on lead CC5 over a total of 915 one minute mean values. The Marquette system read slightly more positive than the tapes on lead CM5 and more negative on lead CC5. In 41 subjects, agreement was maintained within 1 mm, except at peak exercise in eight. This group of 41 showed mean (SD) discrepancies of 0.09 (0.44) mm on CM5 and 0.17 (0.43) mm on CC5 over 777 observations. When the eight peak exercise results were excluded the remaining 33 showed discrepancies of 0.11 (0.37) mm on CM5 and 0.11 (0.36) mm on CC5 over a total of 622 one minute mean values. Again, the Marquette system read more positive than the tapes on lead CM5 and more negative on lead CC5. The remaining three tapes showed disagreements of more than 3 mm that were traced to Q and S wave identification errors in the Marquette system. No significant errors were detected in the tape analyser.

Ambulatory ST depression (groups A2 and A3, fig 1)

Twelve subjects (12.3%) had episodes of significant ST depression (figs 2 and 3). Four women and one man were aged < 40 years (mean 28.2 (4.9)). The remaining five men and two women were aged ≥ 40 (mean 51.4 (7.2)). A total of 31 episodes of ST depression were recorded. There was a range of one to eight episodes per subject (mean 2.5 (2.2)). All 31 episodes were detected in CM5 but only eight were detected in lead CC5. Episodes lasted from one to 32 min (mean 10.0 (9.5) min), with ST segment depression of -0.1 to -2.8 mm. The mean heart rate during the episodes was 122.1 (21.5) beats/min (range 80 to 160) (fig 4). All episodes occurred during the daytime and none occurred during sleep. The subjects' diaries provided information corresponding to the time of ST depression for 15 of the 31 episodes. Seven episodes were associated with car driving, two with heavy lifting, two with cycling, two with brisk walking, one with getting dressed in the morning, and one occurred at rest. Four of these 15 episodes were associated with tobacco smoking. The subjects had not made diary entries for the remaining episodes.

Table 1 Age and sex distribution of 111 subjects

Age range	Men	Women	Total
20–29	16	13	29
30–39	17	6	23
40–49	14	8	22
50–59	15	9	24
60–67	10	3	13

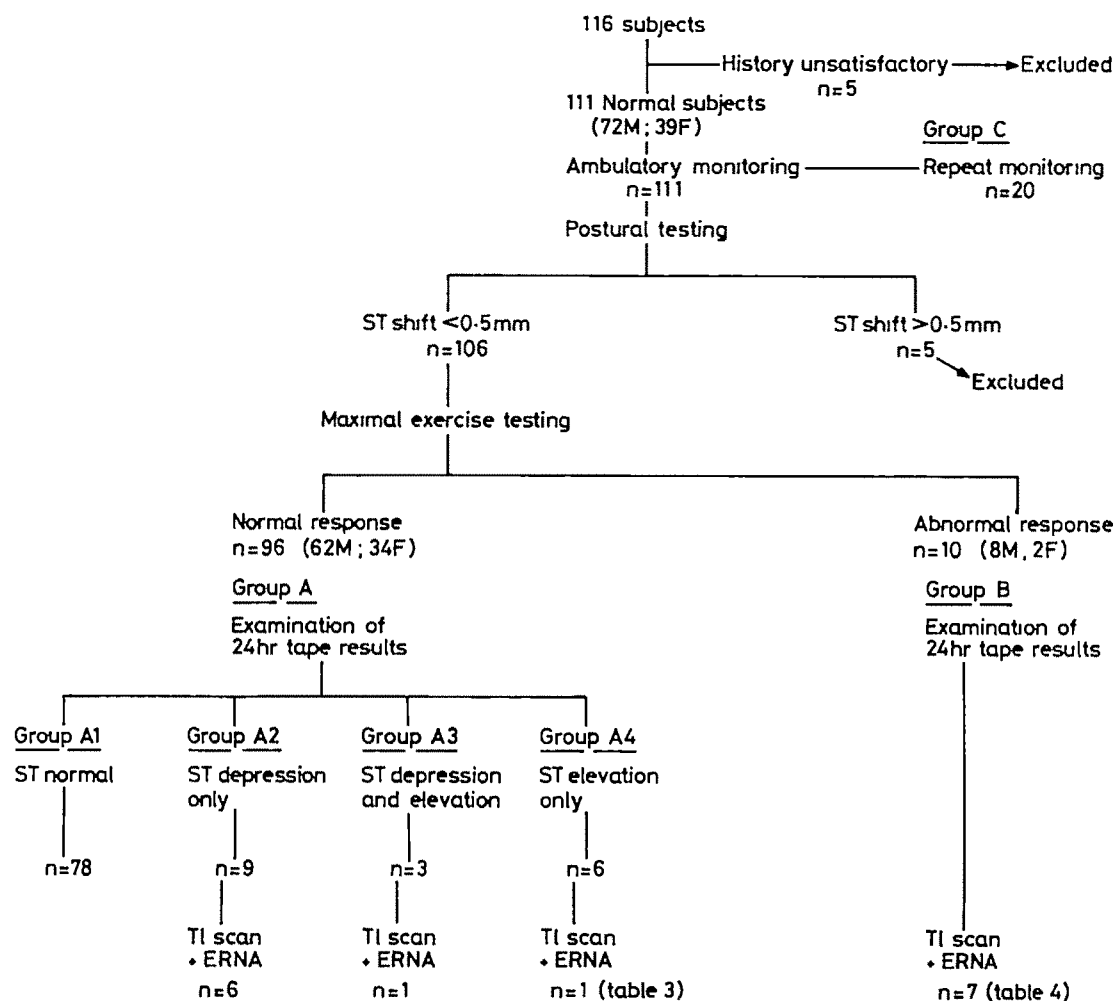


Fig 1 Subject selection and pattern of study. All branches except repeat monitoring are mutually exclusive. ERNA, exercise radionuclide angiography, Tl, thallium.

Ambulatory ST elevation (groups A3 and A4, fig 1)

In most people there was a slight (0.2–0.6 mm) upward shift of the baseline at night. Nine people (six men, three women, aged 21–63 years) showed a more pronounced upward shift in baseline of 0.8–1.2 mm. The upward trend in the baseline followed the downward trend in the heart rate (fig 5).

Nine (9.3%) of the 96 subjects had 28 short distinct episodes of abnormal ST segment elevation 1.0 to 2.5 mm above the prevailing baseline. They were all men aged 25–57 years. Five were aged ≤ 40 years (mean 30.4 (5.6)) and four were > 40 (mean 52.2 (3.7)). The episodes continued for a mean of 25.3 (22.1) min (fig 6). The heart rate ranged from 34 to 78 beats/min (mean 58.1 (13.5)) and remained unchanged during the episodes.

ST elevation and depression (group A3, fig 1)

Three subjects (all men) who showed ST segment depression during the day also had episodes of ST segment elevation at night.

T wave changes

Seventeen individuals showed peaking of the T wave, which was associated with slow heart rates and ST elevation (fig 5). We saw T wave flattening or inversion or both in 17 subjects without ST depression. Four of the subjects with ST depression had associated T inversion (fig 3). Two subjects had both peaking and flattening of the T wave. In all, 32 (33%) subjects showed T wave changes not associated with significant ST shift.

Table 2 Validation of ambulatory tape v CASE system: analysis of differences

		CASE-tape, 1 min mean ST(J) values		
		CM5	CC5	Heart rate (beats/min)
Group 1 (agreement within 0.5 mm throughout exercise) n = 50				
Mean difference (mm)		0.089	-0.073	-0.02
SD		0.193	0.187	3.66
No of observations		900	915	984
Group 2 (agreement within 0.5 mm except around peak exercise) n = 16				
Mean difference (mm)		0.143	-0.009	0.66
SD		0.354	0.297	3.91
No of observations		278	255	300
Group 3 (agreement within 1 mm throughout exercise) n = 17				
Mean difference (mm)		0.079	-0.183	0.39
SD		0.38	0.38	3.14
No of observations		344	365	378
Group 4 (agreement within 1 mm except around peak exercise) n = 8				
Mean difference (mm)		0.048	-0.437	-1.09
SD		0.634	0.583	4.121
No of observations		155	157	168
All subjects (n = 91)				
Mean difference (mm)		0.092	-0.121	0.075
SD		0.329	0.329	3.68
No of observations		1677	1692	1830

CASE, Marquette computer-assisted system for exercise.

Results of radionuclide testing (tables 3 and 4)

Eight of the 18 subjects who showed ST changes on ambulatory monitoring despite a normal exercise test had radionuclide ventriculograms and thallium scanning during exercise. These were six of the nine who had shown ambulatory ST depression alone (group A2), one of the six who had shown ST elevation alone (group A4), and one of the three who had shown both ST depression and elevation (group A3).

The ventriculograms showed evidence of functional impairment in five; left ventricular ejection fraction fell during exercise in two subjects and the resting peak filling rate was at the lower end of normal^{15,16} in four. One of these (a woman of 33) also had an abnormal thallium scan showing a small reversible perfusion defect near the upper interventricular septum. The remaining seven exercise thallium scans were normal, as defined both by the absence of a photon-deficient area and by quantitative washout.

SUBGROUP OF SUBJECTS WITH ABNORMAL EXERCISE RESPONSE (GROUP B, FIG 1)

Ten people (eight men, two women, aged 42–65 years) had an abnormal exercise response on the treadmill; none complained of chest discomfort and the end point was always fatigue. Five had 16 episodes of ST depression during ambulatory monitoring that lasted for 3–5 minutes at heart rates of 100–160 beats/min and one had ST elevation at night (heart rate 50/min). We obtained radionuclide ventriculograms during exercise in seven of the 10 subjects and showed functional impairment in four; the left ventricular ejection fraction did not increase

in any of these four and the resting peak filling rate was low in two. Exercise thallium scans performed in six of these subjects were normal, however (table 4).

REPEAT TAPE ANALYSIS (GROUP C, FIG 1)

We analysed 40 tapes from this subgroup of 20 subjects.

ST baseline levels: repeatability (table 5)

For both leads the difference between day and night was significantly greater than the difference between recordings ($p < 0.001$); this means that the nocturnal shift must be taken into account when computer analysis is performed. Analysing day and night separately, the component of variability within subjects between recordings was significantly less ($p < 0.001$) than that between subjects both for daytime and for night, indicating good individual repeatability of baselines.

ST depression: repeatability (table 6)

A total of 136 episodes of 0.5 mm ST depression at J + 60 ms were detected in lead CM5. The repeatability was good for the total number of episodes detected ($F = 3.5$; $p < 0.001$), the maximal ST depression ($F = 2.6$; $p = 0.03$), and the heart rate at maximal ST depression ($F = 7.2$; $p < 0.001$). The average duration of episodes was poorly repeatable because the component of variability between recordings was similar to that between subjects. A similar result was seen for lead CC5, where 87 episodes were detected.

24 hour ST (J+60) trend

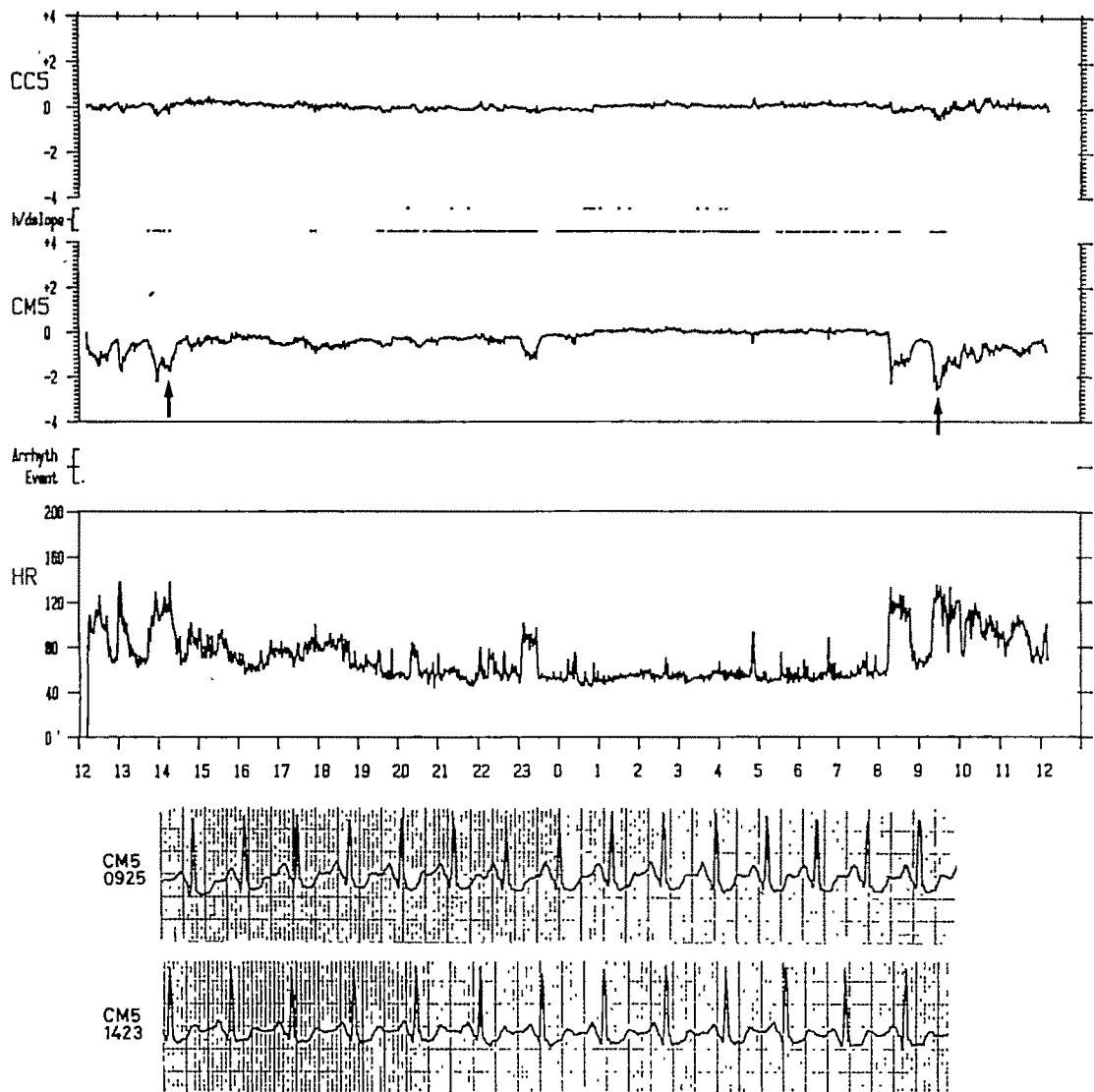
61 F
15.6.84

Fig 2 ST segment trend chart showing horizontal depression in CM5 at 9.25 h and 14.23 h.

ST elevation: repeatability

Episodes of ST elevation were too infrequent in this subgroup of 20 subjects to permit a proper analysis of variance. ST elevation occurred on both recordings in only two subjects in lead CC5 and in only one recording in lead CM5.

Discussion

Ambulatory tape recorders were first introduced for the detection of cardiac arrhythmias¹⁷ but since then they have also been used to detect episodes of myocardial ischaemia. Investigations of the recorder

24 hour ST (J+60) trend

32 M

18.7.84

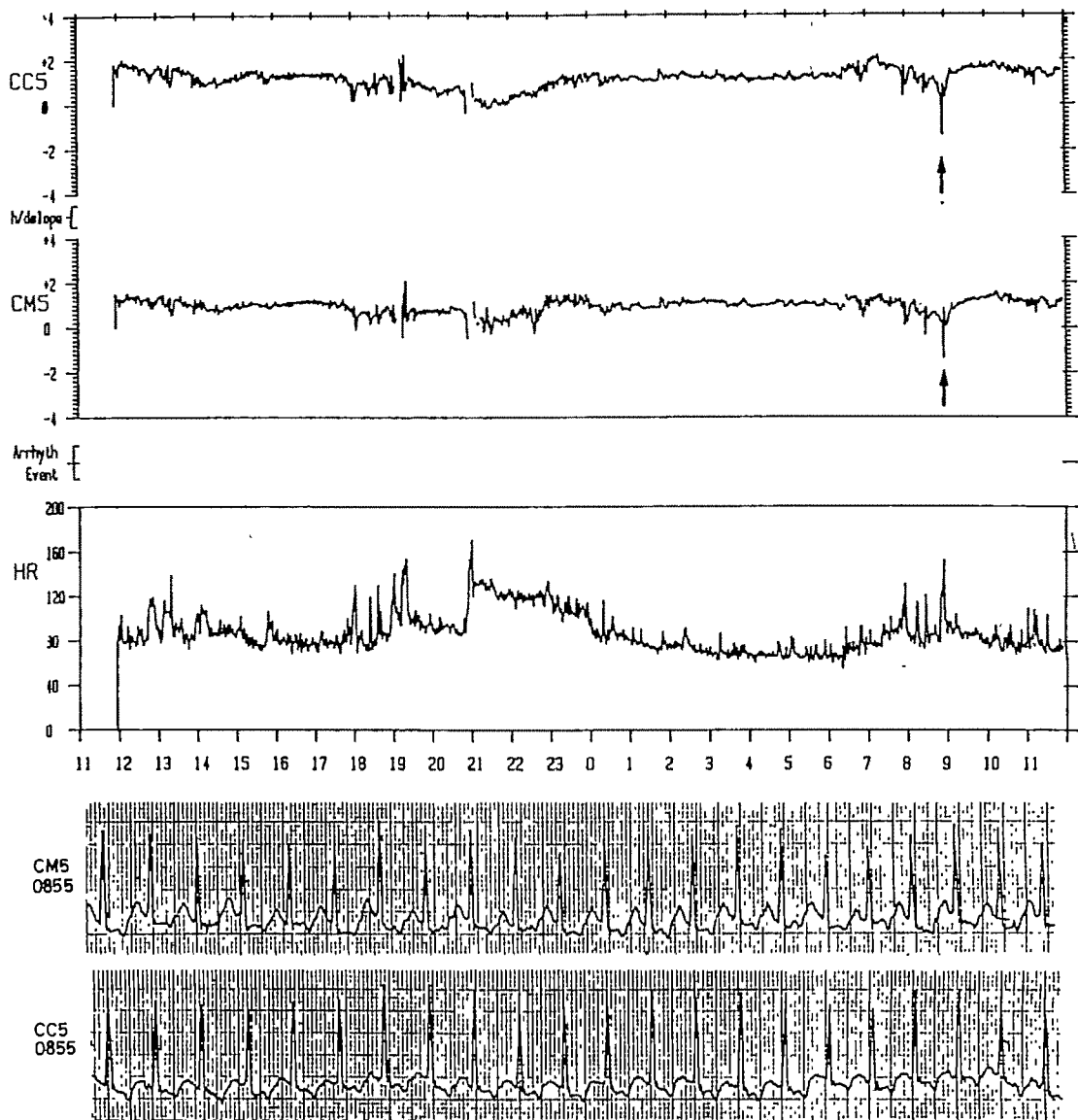


Fig 3 Trend chart showing "ischaemic" ST depression in a young man at 8.55 h during brisk walking.

performance, particularly ST-T fidelity, led to the introduction of frequency modulated recorders for the accurate detection of ST segment shifts.^{8,18,19} Reports of "silent myocardial ischaemia"²⁰ and its potential dangers^{3-5,21} continue to increase despite the fact that exercise ST deviation is a poor predictor of

obstructive coronary artery disease²² and that ST changes can be produced by public speaking,²³ a hot sauna,⁷ gastroscopy,²⁴ mitral valve prolapse,²⁵ neurocirculatory asthenia,²⁶ and car driving.²⁷ It is not clear whether these changes are caused by ischaemia or other mechanisms.

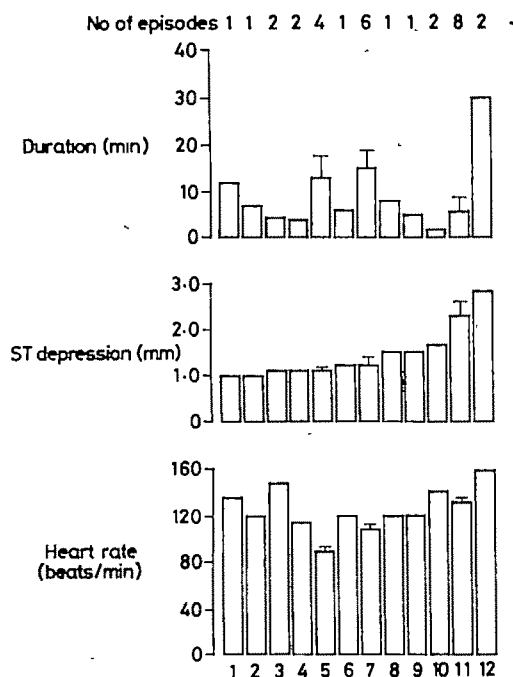


Fig 4 Histograms showing the maximal heart rate, maximal ST depression, and duration of the episodes in individual subjects (mean (SEM)).

Before we can draw conclusions about the degree and incidence of "silent myocardial ischaemia" from ambulatory tape recordings we need to know the behaviour of the ST segment in normal subjects under ambulant conditions. The results of several studies were conflicting, with reports of significant ST segment depression in 0%,²⁸ 2.5%,¹¹ 8.3%,⁹ and 30%¹⁰ of subjects and of ST segment elevation in 0%,²⁸ 5%,¹¹ 23%,⁹ and 0%¹⁰ of subjects respectively.

Several factors could have contributed to this wide variation in results. The most obvious is subject selection; in addition to a pronounced occupational bias in three of the studies,⁹⁻¹¹ the group studied by Armstrong *et al*¹⁰ was older than that of Quyyumi *et al*⁹ or Deanfield *et al*.¹¹ In the last two studies, ST elevation was associated with the younger subjects, but important ST depression had no clear association with age. In the present study we attempted to minimise bias by selecting subjects randomly from a general population and including those aged from 20 to 70 years.

Method differences may also have contributed to the spread of results. Two studies used Avionics direct mode recorders,^{10,28} whereas we, Quyyumi *et al*,⁹ and Deanfield *et al*¹¹ used frequency modulated recorders to avoid possible distortion of the ST-T segment. Armstrong *et al* made recordings on lead

CH6,¹⁰ whereas the other studies used CM5 as the lateral lead. Two groups used CM2 as an auxiliary lead and found it to be less sensitive than CM5 for the detection of ST-T changes.^{9,11} In common with Armstrong *et al*,¹⁰ we recorded CC5 as an auxiliary lead. We found it less sensitive than CM5 for detecting ST depression but more sensitive for detecting ST elevation.

In the four earlier studies, the reported incidence of ambulatory ST changes included subjects with postural and exercise induced ST depression. Moreover, orthostatic and exercise tests were performed only on subgroups of volunteers chosen either at random,¹⁰ or by age¹¹ or because of significant ambulatory ST changes.⁹ In the present study screening of all subjects before the study ensured that the 12 subjects with significant ambulatory ST depression and the nine with ST elevation were free of orthostatic or exercise induced ST segment changes. Such screening would have substantially altered the results of the previous studies, particularly that of Armstrong *et al*.¹⁰

Finally (and perhaps most importantly), though the previous studies all used the same definition of significant ST segment depression, the criteria for episodes were not the same. In particular, Deanfield *et al* excluded any episodes in which baseline instability caused the ST depression to appear intermittent.¹¹ This strict criterion may account for the low incidence of ST depression reported by that group, since in our study almost all episodes of ST depression were accompanied by tachycardia and some baseline instability. Because we were using computer averaged measurements we were confident of the objectivity of our baseline and of the threshold values for detection of episodes. In addition, both observers also had to agree on the visual scoring of each electrocardiographic strip printout before it was accepted as a genuine episode.

There is disagreement about the duration of episodes of ST segment elevation and depression. Our findings agree with previous reports that ST elevation usually occurs at night and at relatively low heart rates. Whereas some workers reported episodes of ST elevation lasting several hours,^{9,11} we saw well defined bursts of ST elevation lasting only a few minutes. This disagreement may arise because other workers did not take into account the slow nocturnal upward baseline shift. We did not find any episodes of ST depression during sleep; all were related to increased heart rates during activities like jogging, cycling, car driving, and smoking recorded on the subjects' diary cards. The incidence of T wave changes in our study accorded with that of Armstrong *et al*,¹⁰ whereas others have reported T wave changes in over half their subjects.¹¹

24 hour ST segment trend

52 M

13.11.84

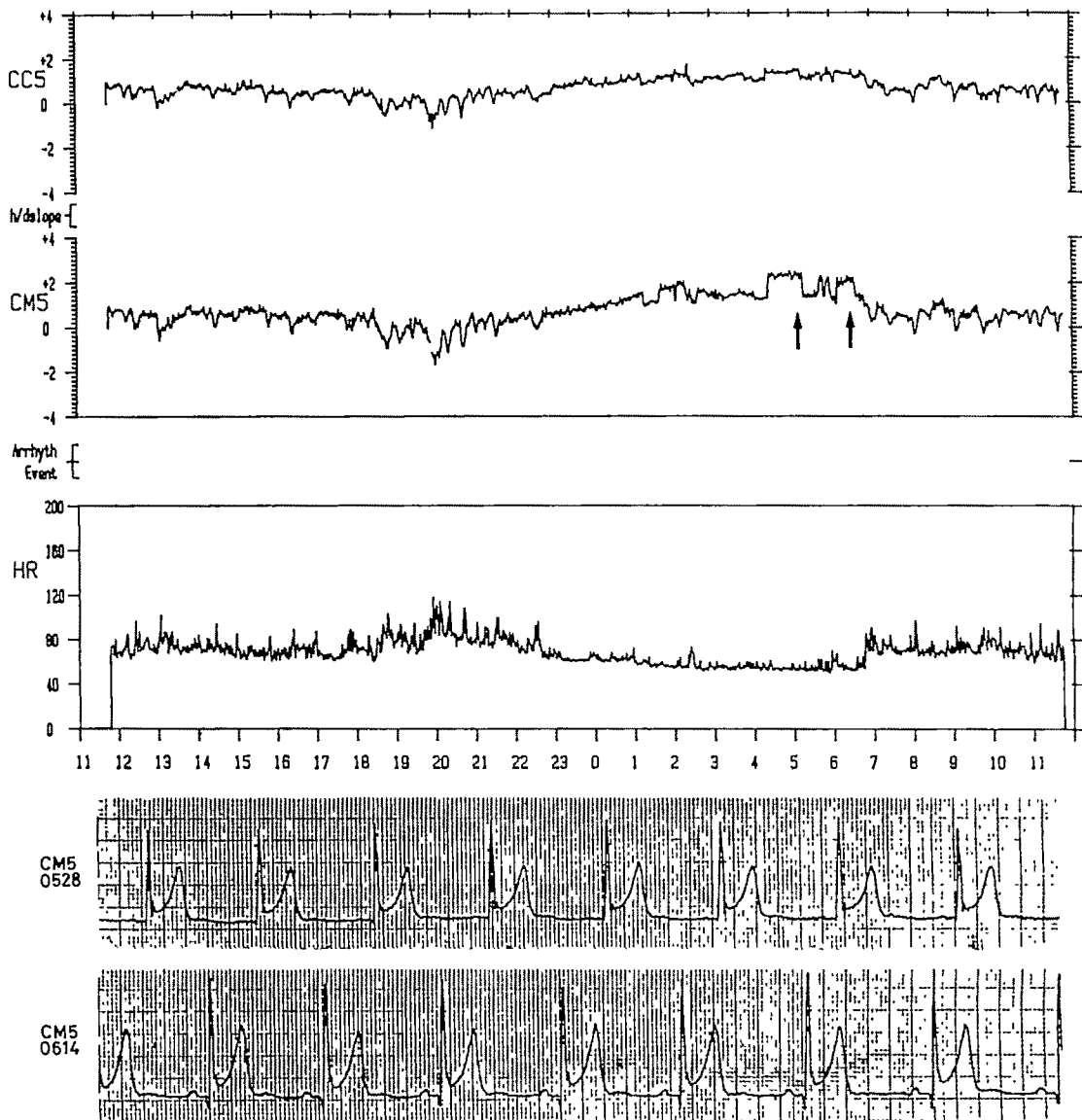


Fig 5 24 hour trend chart showing a gradually rising baseline at night, most apparent in CMS, with distinct episodes of ST elevation superimposed. These occurred during sleep at a heart rate of 53–55 beats/min.

False positive exercise responses in normal people are well documented^{29,30} but we were careful to separate out all subjects with positive exercise responses because they might have occult obstructive coronary disease. Despite our stringent exclusion criteria we saw significant ambulatory ST segment

elevation and depression in 9% and 12% of our subjects respectively. Coronary arteriography was not warranted in these symptom free healthy volunteers, but where possible people with abnormal ST segment depression were investigated by exercise thallium imaging and exercise radionuclide ven-

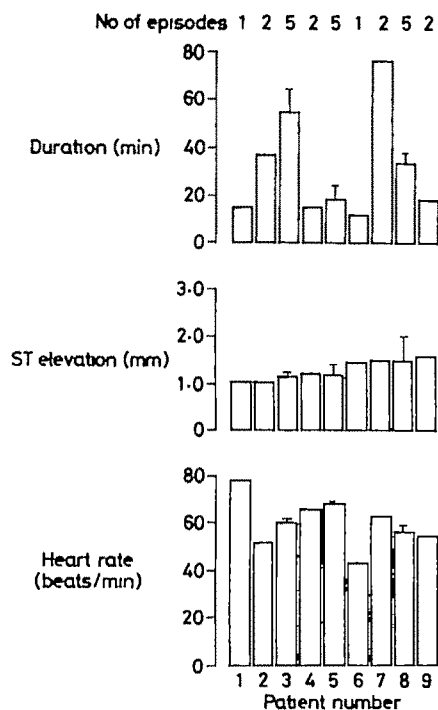


Fig 6 Histograms showing the heart rate, maximal ST elevation, and duration of the episodes in all subjects with ST elevation.

triculography. We found no evidence of significant "occult" obstructive coronary artery disease. Although the ventriculograms detected some impairment of function, our final reference standard of normality was the thallium scan, since this has the greatest diagnostic and prognostic sensitivity for coronary artery disease.^{31,32}

One 33 year old woman had a reversible perfusion defect in the redistribution phase of the thallium scan

in the region of the upper interventricular septum. Her radionuclide angiogram was normal and she was symptom free; we therefore did not think that coronary angiography was justifiable. This woman has remained symptom free for a further two years.

In people with ST segment elevation, coronary vasospasm may have contributed to our findings. But we did not consider it ethical to proceed to provocative testing with cold pressor³³ or ergometrine maleate,^{34,35} since both tests would require coronary arteriography and are of unproven value particularly in symptom free "normal" subjects. These subjects remained symptom free during the two year follow up.

It is interesting that the results of radionuclide testing were broadly the same in people with an abnormal exercise electrocardiographic response and in those with normal exercise responses but ST depression on ambulatory monitoring. In both groups the thallium scans were normal (with one possible exception), while approximately half the ventriculograms showed evidence of functional impairment. This group may represent a very early stage of coronary artery disease; only long term follow up will confirm or refute this notion.

"False positive" ambulatory ST changes have been described by several workers, but because of method limitations it has been impossible to separate genuine ST deviations from artefact. The ST changes observed in our study are unlikely to be artefactual because we validated the accuracy of each individual recording and also took the nocturnal change in the baseline into account in the tape analysis. The subjects who were restudied showed consistent ST baseline levels and repeatable ST changes. A total of 22 subjects showed ST segment abnormalities either during exercise or during monitoring; we were able to perform exercise thallium scans in 14, and 13 of these were normal. In

Table 3 Results of radionuclide testing in eight people who had shown ST changes during ambulatory recording (groups A2, A3, A4, fig 1)

Case No	Sex	ST change	LVEF (%)		PFR (EDV/s)		Wall motion score		Thallium score
			Rest	Exercise	Rest	Exercise	Rest	Exercise	
1	F	D	55	49	1.2	5.5	0	0	0
2	F	D	54	46	3.2	4.1	1	1	0
3	F	D	50	68	2.1	5.7	0	0	Reversible septal defect
4	F	D	Normal*		Normal*		0	0	0
5	F	D	Normal*		Normal*		0	0	0
6	M	D+E	51	59	1.98	6.01	0	0	0
7	M	D	69	75	2.3	7.6	0	0	0
8	M	E	Normal*		Normal*		0	0	0

*Data could not be recovered because of disk corruption; however, all values were reported as normal at the time of acquisition.

LVEF, left ventricular ejection fraction; D, ST depression present on ambulatory recording; E, ST elevation present on ambulatory recording; PFR, peak filling rate; EDV/s, end diastolic volumes per second

Table 4 Results of radionuclide testing in seven out of ten people who had shown a positive electrocardiographic response during exercise (group B, fig 1)

Case No	Sex	LVEF (%)		PFR (EDV/s)		Wall motion score		Thallium score
		Rest	Exercise	Rest	Exercise	Rest	Exercise	
9	F	64	59	2.0	4.8	0	0	0
10	F	61	62	2.7	7.6	0	0	0
11	M	68	80	2.6	4.2	0	0	0
12	M	69	76	2.6	6.8	0	0	0
13	M	65	73	3.4	6.3	0	0	0
14	M	66	62	2.7	2.3	0	0	0
15	M	61	57	2.4	5.8	0	0	—

LVEF, left ventricular ejection fraction; PFR, peak filling rate; EDV/s, end diastolic volumes per second

Table 5 Analysis of variance: ST baseline values in 20 people with recordings on two occasions

Variable	No	Overall mean	σ_s	σ	$F = (\sigma_s/\sigma)^2$	df of σ_s	df of σ	p
CM5 baseline.								
Day (mm)	20	-0.13	0.40	0.14	8.16	19	39	<0.001
Night (mm)	20	+0.31	0.55	0.15	13.44	19	39	<0.001
CC5 baseline								
Day (mm)	17	+0.05	0.20	0.08	6.25	16	33	<0.001
Night (mm)	17	+0.22	0.22	0.11	4.00	16	33	<0.001

Comparison of mean values for day and night

CM5: SE of the difference = 0.046, $t = (0.31 - 0.13)/0.046 = 9.56$, $df = 38$, $p < 0.001$

CC5: SE of the difference = 0.032, $t = (0.22 - 0.05)/0.032 = 5.31$, $df = 32$, $p < 0.001$

σ_s , component of variability between subjects; σ , component of variability between recording occasions; df, degrees of freedom

Table 6 Analysis of variance: episodes of ST depression in 20 people with recordings on two occasions

Variable	No	Overall mean	σ_s	σ	$F = (\sigma_s/\sigma)^2$	df of σ_s	df of σ	p
CM5.								
Total episodes	20	3.4	3.0	1.6	3.51	19	39	<0.001
Episodes on both recordings	11	5.5	2.5	1.5	2.89	10	21	0.02
Maximal ST depression (mm)	11	-0.98	0.24	0.15	2.56	10	21	0.03
Heart rate at maximal ST depression (beats/min)	11	120.1	17.5	6.5	7.25	10	21	<0.001
Average duration (min)	11	22.2	8.5	8.4	1.02	10	21	NS
CC5								
Total episodes	20	2.2	2.7	1.3	4.31	19	39	<0.001
Episodes on both recordings	9	4.2	3.0	1.4	4.86	8	17	0.003
Maximal ST depression (mm)	9	-0.84	0.24	0.07	11.75	8	17	<0.001
Heart rate at maximal ST depression (beats/min)	9	125.9	20.1	11.1	3.28	8	17	0.02
Average duration (min)	9	24.0	13.8	11.8	1.36	8	17	NS

σ_s , component of variability between subjects; σ , component of variability between recording occasions; df, degrees of freedom.

these subjects we felt confident that important obstructive coronary artery disease had been excluded.^{12,36,37} The cause of these shifts in ST segment at all ages and in both sexes remains to be established.

The clinical implications of our findings are important in view of the current emphasis on screening of the population for "occult" or "silent" coronary artery disease and we feel that the results of such screening investigations should be interpreted

with caution.

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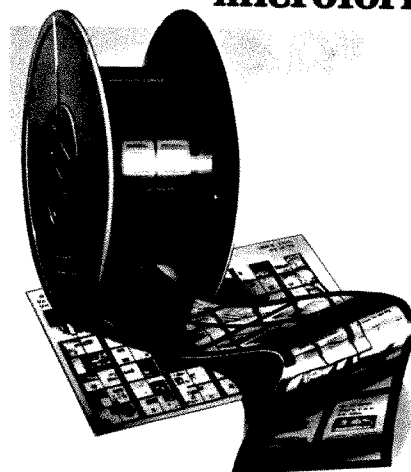
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Time course of ventricular arrhythmias and the signal averaged electrocardiogram in the post-infarction period: a prospective study of correlation

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SUMMARY The incidence and time course of complex ventricular arrhythmias and of the abnormal signal averaged electrocardiogram were studied prospectively in 90 patients in the first two months after acute myocardial infarction. Serial recordings of both 24 hour ambulatory and signal averaged electrocardiograms were obtained 0-5 days (phase 1), 6-30 days (phase 2), and 31-60 days (phase 3) after infarction. A total of 264 ambulatory electrocardiograms and 264 signal averaged electrocardiograms were available for analysis. Complex ventricular arrhythmias were seen in 31%, 17%, and 38% of patients during phases 1, 2, and 3 respectively, and abnormal signal averaged electrocardiogram in 13%, 24%, and 16%. The incidence of complex ventricular arrhythmias was not significantly different in patients with or without an abnormal signal averaged electrocardiogram in the entire study period nor in any of the three phases after infarction. During phase 2 when abnormal signal averaged electrocardiograms were most common complex ventricular arrhythmias were least common.

This lack of correlation suggests that the abnormal signal averaged electrocardiogram and complex ventricular arrhythmias after infarction have different electrophysiological bases.

Indices of left ventricular dysfunction¹⁻⁴ and electrical instability^{2,3,5-9} are the strongest predictors of mortality after infarction. Three markers for electrical instability have commonly been investigated: (a) spontaneous ventricular arrhythmias during long term ambulatory electrocardiographic recording,^{1-3,5-7} (b) ventricular tachycardias induced by programmed electrical stimulation,^{1,8-11} and (c) late potentials detected on the signal averaged electrocardiogram.^{9,11-14} The prognostic significance of arrhythmias elicited by programmed stimulation remains controversial.¹⁵ On the other hand, complex ventricular arrhythmias on the ambulatory electrocardiogram have shown independent correlation with sudden death in several large multicentre studies.^{2,3,7} The role of the signal averaged electrocardiogram for identifying patients at risk of sudden

death after myocardial infarction has been recently emphasised.^{9,11,12,14}

Most studies have analysed single recordings of the ambulatory and signal averaged electrocardiograms obtained at different times after infarction. We prospectively studied the correlation between the incidence and time course of complex ventricular arrhythmias and late potentials during the first two months after infarction by analysing serial records of the 24 hour ambulatory electrocardiogram and the signal averaged electrocardiogram.

Patients and methods

PATIENTS

The criteria for inclusion in the study were: (a) a diagnosis of acute myocardial infarction, confirmed by clinical and electrocardiographic criteria and by an increase in serum concentrations of cardiac enzymes (creatinine kinase MB); (b) the absence of bundle branch block on the standard electrocardiogram; (c) completion of the study. We studied 90

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patients (63 men and 27 women aged 30–81 (mean (SD) 59.2 (13.4)) between October 1985 and March 1987. Serial recordings were obtained in the first two months after infarction: (a) 0–5 days after infarction (phase 1); (b) 6–30 days after infarction (phase 2); (c) 31–60 days after infarction (phase 3). An ambulatory electrocardiogram and a signal averaged electrocardiogram were obtained within a 24 hour period during each of the three phases. Surviving patients had recordings during all three phases. The myocardial infarction was anterior in 54 (60%) patients, inferior in 29 (32%), and non Q-wave in seven (8%). A previous myocardial infarction was suggested by history or electrocardiogram or both in 11 (12%) patients.

SIGNAL AVERAGED ELECTROCARDIOGRAM

The signal averaged electrocardiogram was recorded with the Arrhythmia Research Technology model 101PCD electrocardiograph by methods described by Simson.¹⁶ The electrocardiogram was recorded during sinus rhythm with standard bipolar orthogonal X, Y, and Z leads. Signals were amplified, averaged, and filtered with a bidirectional filter at frequencies of 25–250 Hz. The filtered leads were then combined into a vector magnitude ($\sqrt{X^2 + Y^2 + Z^2}$). A computer program algorithm determined the onset and offset of the QRS complex and calculated the total filtered QRS duration and the root mean square voltage of the signals in the last 40 ms of the filtered QRS. The duration of low amplitude signals $<40 \mu\text{V}$ was also calculated but was not used for analysis. Recordings with a noise level $\geq 1 \mu\text{V}$ were rejected. A total of 264 signal averaged electrocardiograms with a mean (SD) noise level of 0.484 (0.179) μV were considered for analysis. Late potentials were defined as low amplitude signals in the last 40 ms of the filtered QRS with a root mean square voltage $\leq 25 \mu\text{V}$. An abnormal signal averaged electrocardiogram was defined as a recording showing the presence of late potentials or a total filtered QRS duration ≥ 120 ms or both.¹⁶

AMBULATORY ELECTROCARDIOGRAM

A two channel, 24 hour electrocardiogram was recorded with the Avionics (model 445) portable units and analysed with the Avionics (model Evaluator II 9500A) replay unit. Arrhythmia detection was validated by one of the investigators. Complex ventricular arrhythmias were classified as frequent ventricular premature complexes ($\geq 10/\text{hour}$); non-sustained ventricular tachycardia (≥ 3 ventricular premature complexes lasting <30 seconds at a rate $<100/\text{min}$); and sustained ventricular tachycardia (lasting ≥ 30 s). The incidence of ventricular fibrilla-

tion during the first five days after infarction was also assessed and a correlation with the signal averaged electrocardiogram was sought.

STATISTICAL ANALYSIS

We used the χ^2 test to analyse the incidence of complex ventricular arrhythmias in patients with or without an abnormal signal averaged electrocardiogram. We used Yates' correction for continuity or Fisher's exact test when appropriate.¹⁷ A probability (p) value <0.05 was considered to be statistically significant.

Results

INCIDENCE OF ABNORMAL SIGNAL AVERAGED ELECTROCARDIOGRAMS AND COMPLEX VENTRICULAR ARRHYTHMIAS

Phase 1 (0–5 days after infarction)—The signal averaged electrocardiogram and the 24 hour ambulatory electrocardiogram were obtained in all 90 patients enrolled in the study. The signal averaged electrocardiogram was abnormal in 12 (13%) patients and complex ventricular arrhythmias were recorded during the ambulatory electrocardiogram in 28 (31%) patients. The ambulatory electrocardiogram showed frequent ventricular premature complexes in 21 (23%) patients, non-sustained ventricular tachycardia in 16 (18%), and sustained ventricular tachycardia in one (1%). On the other hand, ventricular fibrillation occurred in 7 (8%) patients, two with and five without complex ventricular arrhythmias on the ambulatory electrocardiogram. All episodes of ventricular fibrillation occurred within 48 hours of admission and cardioversion was success in all of them. The incidence of complex ventricular arrhythmias on the ambulatory electrocardiogram was not statistically different in patients with or without an abnormal signal averaged electrocardiogram (50 v 28%). None of the patients who developed ventricular fibrillation had an abnormal signal averaged electrocardiogram.

Phase 2 (6–30 days after infarction)—The signal averaged and 24-hour ambulatory electrocardiograms were obtained in 89 patients. One patient with an abnormal signal averaged electrocardiogram in phase 1 died of electromechanical dissociation as the terminal event in cardiogenic shock on the eighth day after infarction. The incidence of an abnormal signal averaged electrocardiogram was higher in phase 2 than in phase 1 (21 cases, (24%) whereas the incidence of complex ventricular arrhythmias on the ambulatory electrocardiogram was lower (15 cases, (17%)). Frequent ventricular premature complexes occurred in 12 (13%) patients, non-sustained ventricular tachycardia in five (6%), and sustained

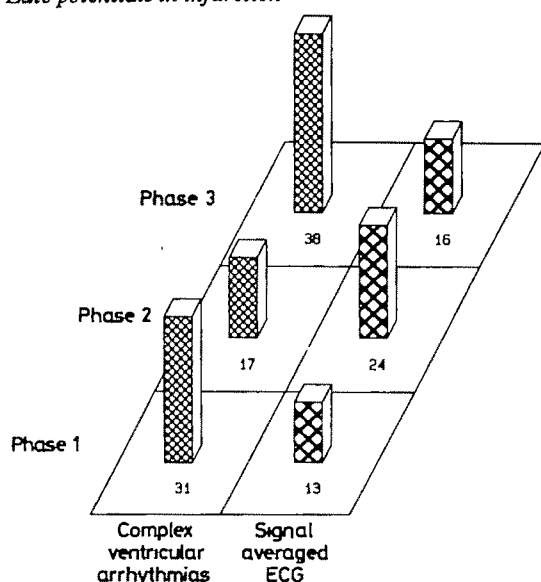


Fig 1 Frequency of complex ventricular arrhythmias and an abnormal signal averaged electrocardiogram in patients after acute myocardial infarction.

ventricular tachycardia in one (1%). As in phase 1, the incidence of complex ventricular arrhythmias was not statistically different in patients with or without an abnormal signal averaged electrocardiogram (19% v 16%).

Phase 3 (31–60 days after infarction)—The signal averaged and 24 hour ambulatory electrocardiograms were recorded in 85 patients. There were four cardiac deaths: one was caused by incessant ventricular tachycardia in a patient with an abnormal signal averaged electrocardiogram and three were not sudden and occurred in two patients with and one patient without an abnormal signal averaged electrocardiogram. The incidence of an abnormal signal averaged electrocardiogram was lower than in phase 2 (14 cases, (16%)), while complex ventricular arrhythmias were more frequent on the ambulatory electrocardiogram (33 patients, (38%)). Frequent ventricular premature complexes occurred in 28 (33%) patients, non-sustained ventricular tachycardia in 12 (14%) patients, and sustained ventricular tachycardia in one (1%) patient. As in phases 1 and 2, the incidence of complex ventricular arrhythmias was not statistically different in patients with or without an abnormal signal averaged electrocardiogram (57% v 35%).

Figure 1 summarises the incidence of complex ventricular arrhythmias and an abnormal signal averaged electrocardiogram during the three post-infarction phases. The figure shows that complex

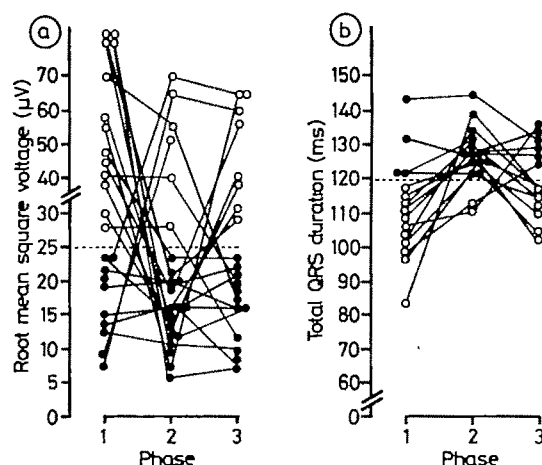


Fig 2 Variables measured on signal averaged electrocardiogram in the patients who had one or more abnormal recordings. Changes in the low amplitude signals in the last 40 ms of the filtered QRS complex (a) and in the total duration of the filtered QRS (b) in serial recordings obtained 0–5 days, 6–30 days, and 31 to 60 days after infarction are shown. The horizontal dashed lines indicate the criteria for an abnormal signal averaged electrocardiogram. See text for detail.

ventricular arrhythmias were common in the first five days after infarction, became less frequent between six and 30 days, and showed a late increase during the second month after myocardial infarction. Conversely, the incidence of an abnormal signal averaged electrocardiogram reached a maximum between six and 30 days after infarction.

TIME COURSE OF THE ABNORMAL SIGNAL AVERAGED ELECTROCARDIOGRAM

An abnormal signal averaged electrocardiogram was seen during one or more of the post-infarction phases in 28 (31%) patients (a late potential ($n = 13$), a long filtered QRS ($n = 5$), or both ($n = 10$)). The recording returned to normal in 42% of the patients within 60 days of infarction. An abnormal recording was more common in patients with inferior infarction

Table 1 Time course of the abnormal signal averaged electrocardiogram in acute myocardial infarction

Phase 1	Phase 2	Phase 3	Number of patients (%)
Yes	Yes	Yes	6 (25)
Yes	Yes	No	1 (4)
Yes	No	No	2 (8)
No	Yes	Yes	5 (21)
No	Yes	No	7 (29)
No	No	Yes	3 (13)

Yes, signal averaged electrocardiogram abnormalities present; No, signal averaged electrocardiogram abnormalities absent.

(14 (48%) of 29 patients) than in those with anterior infarction (14 (26%) of 54). All five patients with a signal averaged electrocardiogram showing an abnormal QRS duration had anterior infarction. The evolution of abnormalities on the signal averaged electrocardiogram was investigated in 24 out of the 28 patients with an abnormal recording who underwent serial studies in all three post-infarction phases (fig 2). The table shows the results of this analysis. The number of abnormal signal averaged electrocardiograms was highest during phase 2 (19 cases). Fifty percent of the patients had only one abnormal recording (fig 3)—25% had two abnormal recordings and 25% had abnormalities in all three signal averaged electrocardiograms.

CORRELATION BETWEEN THE AMBULATORY AND SIGNAL AVERAGED ELECTROCARDIOGRAMS IN INFERIOR AND ANTERIOR MYOCARDIAL INFARCTIONS

Because abnormal signal averaged electrocardiograms were more common in patients with inferior infarction than in those with anterior infarction, we examined the correlation between abnormal signal averaged electrocardiogram and complex ventricular arrhythmias separately in these two groups. In patients with inferior infarction the incidence of complex ventricular arrhythmias was not statistically different in patients with or without an abnormal signal averaged electrocardiogram (50% *v* 22% in phase 1, 0 *v* 18% in phase 2, 50% *v* 39% in phase 3).

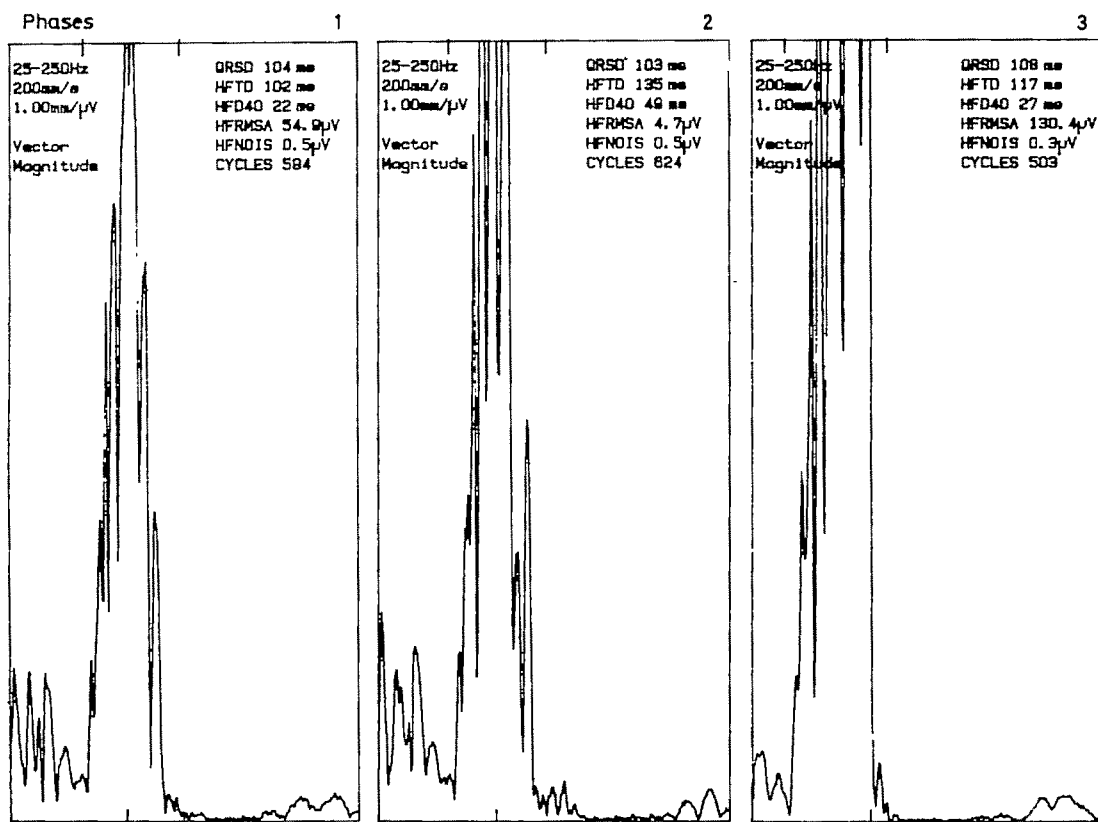


Fig 3 Time course of the signal averaged electrocardiogram in a patient with acute anterior wall myocardial infarction. The vector magnitude recordings of the filtered QRS complex are shown. The three recordings from left to right were obtained, 4, 9 and 35 days after infarction respectively. Abnormalities in the signal averaged electrocardiogram were first seen in the record obtained nine days after infarction as a low amplitude signal in the last 40 ms of the filtered QRS of 4.7 μ V and a filtered QRS complex lasting 135 ms. The recording became normal by the 35th day after infarction. QRSD, QRS duration; HFTD, high frequency total QRS duration; HFD40, duration of high frequency low amplitude signals (< 40 μ V); HFRMSA, high frequency root mean square voltage of signals in the last 40 ms of the high frequency QRS; HFNOIS, high frequency noise level; Cycles, number of averaged QRS complexes.

Similarly, in patients with anterior infarction the incidence of complex ventricular arrhythmias was not statistically different in patients with or without an abnormal signal averaged electrocardiogram (50% v 31% in phase 1, 40% v 16% in phase 2, 67% v 33% in phase 3).

ANTIARRHYTHMIC DRUGS

Exception for two patients who developed sustained ventricular tachycardia and were given a total of four different antiarrhythmic drugs, the only two antiarrhythmic agents that were used throughout the study were lignocaine and β blockers. Lignocaine was given to seven patients for variable periods during their stay in the coronary care unit. The ambulatory and signal averaged electrocardiograms were always recorded while the patients were not receiving lignocaine. Thirty patients were given β blocking drugs at the discretion of their attending physician during the study period. No attempt was made to obtain the recordings when these patients were not taking β blocking drugs.

CLINICAL OUTCOME

There were five cardiac deaths during the study period; four were not sudden and the fifth was caused by incessant ventricular arrhythmia. An abnormal signal averaged electrocardiogram was recorded in four of the five patients including the one with the ventricular arrhythmia. After discharge from hospital, ventricular tachycardia that responded to antiarrhythmic drug treatment developed in a sixth patient with a normal signal averaged electrocardiogram.

Discussion

INCIDENCE AND TIME COURSE OF ABNORMAL SIGNAL AVERAGED ELECTROCARDIOGRAM IN THE POST-INFARCTION PERIOD

The reported incidence of an abnormal signal averaged electrocardiogram in the post-infarction period varied widely in different studies.^{9,12,14} This could be because of: (a) differences in the recording technique and in the definition of an abnormal recording; (b) the time of the recording in the post-infarction period; and (c) the difference in the incidence of late potentials between anterior and inferior infarctions.

The present study emphasises the importance of the time of recording of the signal averaged electrocardiogram in the post-infarction period. The dynamic nature of abnormalities in the signal averaged electrocardiogram shows the limitations of investigations based on a single recording in the post-infarction period. The present study suggests that

the optimal time for signal averaging is between six and 30 days after infarction, rather than in the first five days. When the recording is obtained for the first time during the second month after infarction a significant number of abnormalities will be missed. Late potentials may behave in an even more dynamic way than that shown in the present study. In a preliminary report from our laboratory, serial signal averages were obtained from ambulatory electrocardiograms.¹⁸ Some patients showed variations of the signal averaged electrocardiographic variables with a 24 hour period. The prognostic significance of transient and more lasting abnormalities in the signal averaged electrocardiogram has yet to be established.

CORRELATION BETWEEN THE ABNORMAL SIGNAL AVERAGED ELECTROCARDIOGRAM AND COMPLEX VENTRICULAR ARRHYTHMIAS

The correlation between an abnormal signal averaged electrocardiogram and complex ventricular arrhythmias from serial recordings in the post-infarction period has not been examined before. Several studies have analysed the relation of a single recording of the signal averaged electrocardiogram to complex ventricular arrhythmias detected by telemetry or the ambulatory electrocardiographic recording or both. In one study, the incidence of high grade ventricular ectopy (Lown grade III to V) was similar in post-infarction patients with or without an abnormal signal averaged electrocardiogram, while non-sustained ventricular tachycardia was slightly more common in the group with a normal recording.¹⁴ In a previous study from our laboratory an abnormal signal averaged electrocardiogram was more frequent in patients with complex ventricular arrhythmias than in those without.¹³ Differences in method may account for the apparent discrepancy between the previous study and the present report. In the earlier study, no attempt was made to separate early and late complex ventricular arrhythmias or to synchronise electrocardiographic and signal averaged recordings.

The lack of correlation between an abnormal signal averaged electrocardiogram and complex ventricular arrhythmias detected on the ambulatory electrocardiogram may be explained by differences in the electrophysiological bases for the two phenomena. Late potentials represent ischaemic myocardial zones with delayed activation that can provide the electrophysiological basis for re-entrant rhythms.¹⁹ On the other hand, the underlying electrophysiological mechanism(s) for complex ventricular arrhythmias in the ambulatory electrocardiogram may include reentry and abnormal or triggered automaticity. Complex ventricular arrhythmias caused by focal pacemaker discharge rather than re-

entry are not expected to be associated with late potentials. Moreover, ventricular tachycardia of non-reentrant origin may occur in a heart showing late potentials and does not have a cause and effect relation with the late potentials.

CLINICAL IMPLICATIONS

The present study was not designed to determine the long term prognostic significance of the signal averaged electrocardiogram and the ambulatory electrocardiogram in the post-infarction period. None the less, the study suggests that abnormalities in the signal averaged electrocardiograms and complex ventricular arrhythmias in the post-infarction period are independent phenomena and may reflect different electrophysiological conditions. This raises the possibility that the combined use of both non-invasive techniques could provide a better risk stratification for predicting serious arrhythmic events. The optimal time for the recordings and the best technique for recording and analysing the signal averaged electrocardiogram are two issues that need further investigation.

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Effects of coronary artery surgery on left ventricular performance, segmental wall movement, and exertional ischaemia

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SUMMARY The effects of coronary artery surgery on left ventricular performance were assessed serially by echocardiography and treadmill exercise testing in 54 patients. Patients were assessed one day before operation and again before patients left hospital (mean 10 days after operation) and one month and six months after operation. At the predischARGE assessment, 41 (77%) patients showed new abnormalities of left ventricular segmental wall movement, chiefly antero-septal hypokinesia with hyperkinesia of the posterolateral segment. Although there were no significant changes in antero-septal wall thickening after operation, there was a significant increase in posterior wall thickening at all postoperative assessments. The frequency of this abnormality decreased progressively after operation; it persisted in 19 (35%) patients at six months. Left ventricular fractional shortening decreased after operation and at one month was significantly less than before operation. There were no significant changes in left ventricular diastolic diameter during the study. Haemodynamic function during exercise, the duration of exercise, and features of reversible myocardial ischaemia all improved progressively and significantly after coronary artery surgery.

Abnormalities in left ventricular segmental wall movement and thickening commonly develop early after coronary artery surgery but tend to resolve by six months and do not seem to impair left ventricular contractility at rest or exercise performance and haemodynamic function. Recognition of these echocardiographic changes may be clinically important in the assessment of patients after cardiac surgery.

Left ventricular function is an important prognostic factor after coronary artery surgery.^{1,2} Most studies have reported that coronary artery surgery is effective in relieving angina pectoris,^{3,4} but its effects on left ventricular function and wall movement are unclear because studies of this aspect give conflicting results. Whereas some investigators noted post-operative improvements in overall left ventricular function, regional wall motion, and ejection fraction,³⁻⁷ others found no change or even a deterioration in these variables.⁸⁻¹⁰ Abnormal interventricular septal motion has been reported to be common after open heart surgery^{11,12} but the

reasons for this and their influence on left ventricular performance during exercise are obscure.

The aims of this study, therefore, were:

(a) To investigate the serial effects of coronary artery surgery on left ventricular performance and segmental wall movement and thickening.

(b) To assess the incidence of new wall movement abnormalities and their potential importance on exercise performance and haemodynamic function.

(c) To examine the relation between new abnormalities of left ventricular wall movement and residual or recurrent exercise induced myocardial ischaemia.

Patients and methods

We studied 54 patients (50 men and four women, aged 38-72 (mean 53)) admitted for coronary artery surgery. All patients had angina pectoris refractory

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to optimum medical treatment. Nineteen (35%) patients had not had a myocardial infarction, 32 (59%) had had one myocardial infarction, and three (6%) had had two myocardial infarctions. Coronary artery disease was defined as a $> 50\%$ reduction in luminal diameter. Thirty (56%) had three vessel disease, 18 (33%) had two vessel disease, and six (11%) had single vessel disease. Of the 30 patients with three vessel disease, all had saphenous vein grafting and four had internal mammary grafts applied to the left anterior descending coronary artery. Of the 18 patients with two vessel disease, all had saphenous vein grafts and one had an internal mammary graft to the left anterior descending artery. Of the six patients with single vessel disease of the left anterior descending artery, four had internal mammary grafts and two had saphenous vein grafts. These patients were selected from a larger group of patients routinely admitted for coronary artery surgery. The patients included in this study were those who were willing and able to undergo exercise testing and echocardiography before and serially after operation. Six patients were not considered physically fit enough for exercise testing at the pre-discharge assessment (mean 10 days after operation) and two of these were also not assessed at one month. The numbers of patients investigated at each of the four serial assessments were therefore: 54, 48, 52, and 54 respectively.

Echocardiography and symptom limited treadmill exercise testing were performed the day before coronary artery surgery and repeated before patients left hospital and one month and six months after operation.

ECHOCARDIOGRAPHY

The M mode and cross sectional echocardiograms (Hewlett-Packard 77020 AR ultrasonoscope) were performed before exercise testing with the patient supine and in varying degrees of the left lateral decubitus position. Each echocardiographic study included standard views from parasternal, apical, and subcostal transducer positions. The M mode echocardiograms were recorded at a paper speed of 50 mm/s and the cross sectional echocardiograms on a 1/2 inch video tape with a VO 5630 Sony videorecorder for redisplaying the images taken. M mode echocardiograms were obtained by recording the left ventricle at the level of the chordae tendineae to measure the short axis dimensions and fractional shortening. Left ventricular cross sectional echocardiographic images were obtained by recording short and long axis scans through the basal, mid-ventricular, and apical regions of the left ventricle and also two and four chamber apical views.

For the purposes of analysis, the left ventricle was divided into nine segments (fig 1). Most segments

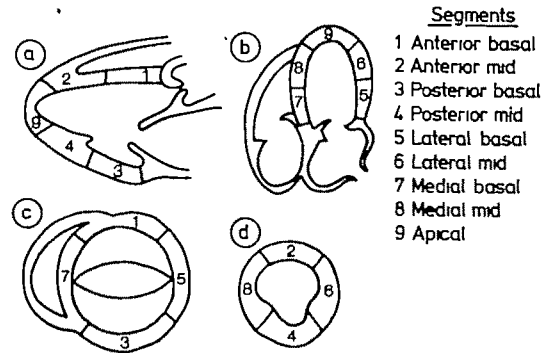


Fig 1 Left ventricular segments derived from echocardiographic views in the (a) long axis parasternal, (b) apical four chamber, (c) parasternal short axis at the level of the mitral valve, and (d) parasternal short axis below the mitral valve cusps

could be identified from more than one transducer position. The wall movement for each segment was classified and scored as hyperkinetic (score 3), normal (score 2), hypokinetic (score 1), akinetic (score 0), and dyskinetic (score -1) on the basis of a visual assessment of endocardial movement during systole. Wall thickening in each segment was scored in each segment as normal (score 2), reduced ($\geq 50\%$ reduction in wall thickening compared with normal segments) (score 1), or absent (no systolic thickening or systolic thinning) (score 0).

The echocardiograms were scored independently by two observers with a third acting as an arbiter when necessary. The two principal observers agreed completely on the scores on 47 patients. Intraobserver variation measured in a random selection of echocardiograms was 11% and 8% for the two observers and this was considered acceptable.

EXERCISE TESTING

Fasting patients performed a symptom limited exercise test (modified Bruce treadmill protocol). A 12 lead electrocardiogram was recorded before exercise and every three minutes during exercise, at peak exercise, at the onset of angina, and every minute during the five minute recovery period or until the electrocardiogram trace had returned to its pre-exercise appearance. A three channel rhythm strip was recorded continuously at a paper speed of 5 mm/s for five minutes before and immediately after exercise (with the patient sitting) and throughout the exercise test. Exercise was stopped if the patient developed severe angina, dyspnoea, fatigue, claudication, dizziness, an abnormal blood pressure response (a fall in systolic blood pressure of ≥ 20 mm Hg), serious ventricular arrhythmias ($>$ six consecutive ventricular extrasystoles), or repeated and frequent

Left ventricular function after coronary artery surgery
(> 30 /minute) ventricular extrasystoles, or ≥ 4 mm of ST segment depression.

DRUGS

At the preoperative assessment, 46 patients were taking β blockers, 48 patients were taking nitrates, and 39 patients were taking a calcium antagonist. At the assessments before leaving hospital and one month after operation no patients were taking any antianginal medication. At the six month exercise test two patients were taking nitrates.

STATISTICAL ANALYSIS

We used analysis of variance for a repeated measures design (to take account of the different numbers of patients at assessments) and the sign test to analyse the exercise test variables. We used Student's paired t test and the χ^2 test to compare echocardiographic assessments of left ventricular wall movement and thickening

Results

EXERCISE TESTING

Exertional angina

Exertional angina was significantly ($p < 0.001$) less common at all three postoperative exercise tests (2%, 10%, and 17%) than preoperatively (65%).

Exertional ST depression

Similarly, exertional ST depression (fig 2) at all postoperative assessments (20%, 19%, 24%) was

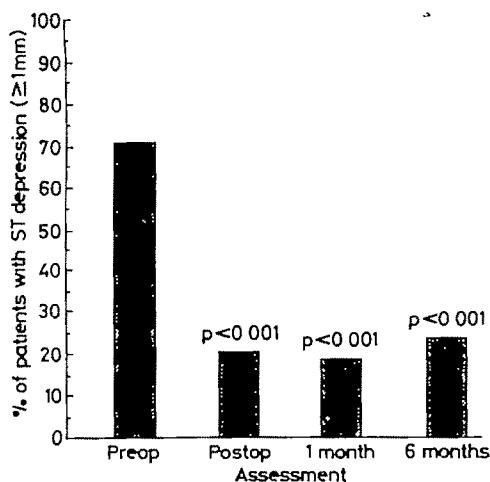


Fig 2 Frequency of ST depression during four serial exercise tests. The p values show the significance of the differences from preoperative values.

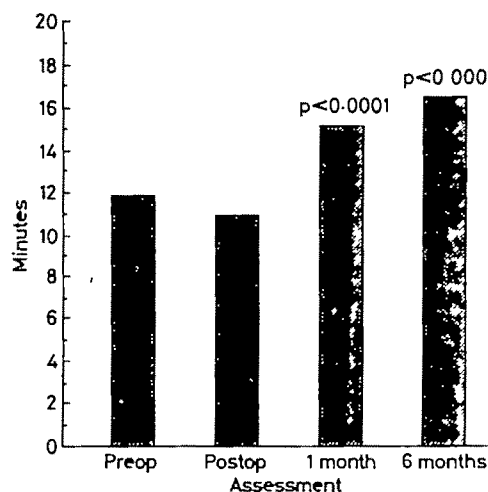


Fig 3 Duration of exercise in minutes at the four serial exercise tests. The p values show the significance of the differences from preoperative values.

significantly less ($p < 0.001$) common than before operation (71%).

Exercise duration

The duration of exercise was slightly shorter during the predischarge test (from 11.9 to 11.0 minutes), but exercise was stopped by leg fatigue and not by angina. At one and six months postoperatively the duration of exercise was significantly increased (from 15.2 to 16.5 minutes, $p < 0.0001$) (fig 3).

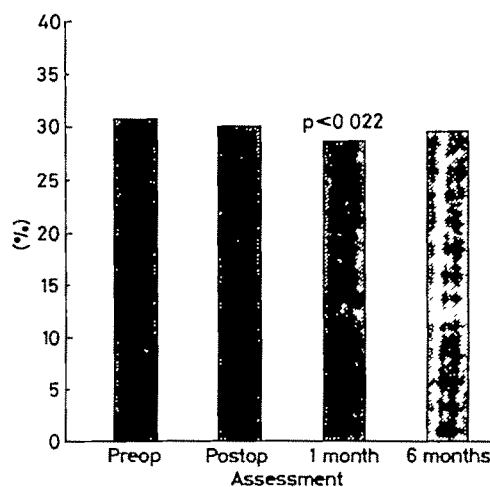


Fig 4 Delta diastolic diameter (left ventricular fractional shortening) at the four serial echocardiographic assessments. The p value shows the significance of the difference from preoperative values

Table 1 Abnormalities of segmental wall motion

	Preop No (%)	Postoperative values		
		Pre-discharge No (%)	1 month No (%)	6 months No (%)
Segments	324	279	351	342
Hyperkinetic	9 (3)	64* (23)	108* (31)	50* (15)
Normal	242 (76)	102* (38)	109* (31)	207 (61)
Hypokinetic	42 (13)	15† (5)	9† (3)	17† (5)
Akinetic	24 (7)	22 (8)	15 (4)	16 (5)
Dyskinetic	7 (2)	76* (27)	110* (31)	52* (15)

Comparisons with preoperative values: * $p < 0.001$; † $p < 0.005$.

Haemodynamic function during exercise

Heart rate at peak exercise rose after operation and at all time points remained higher than preoperative values.

There was also a significant rise in the heart rate-systolic blood pressure double product at peak exercise at all postoperative times.

ECHOCARDIOGRAPHY

Left ventricular dimensions

Although there were no changes in the short axis left ventricular diastolic diameter (M mode) during the study, the left ventricular fractional shortening (delta diastolic diameter) showed a slight decrease one month after operation. This was significantly different from the preoperative value (31.0% to 28.8%, $p = 0.0216$, fig 4).

Segmental wall analysis

Good quality cross sectional echocardiograms of all segments were obtained in 36 patients before operation, in 31 patients after operation and predischage, and in 38 and 39 patients at one and six months after operation. There were data for comparative analysis of segmental wall movement and thickening in 26 patients before operation and before discharge after operation; in 30 preoperatively and at one month after operation; in 30 before operation and one month

after operation; and in 23 patients before operation and six months after operation.

Tables 1-5 summarise the effects of coronary artery surgery on segmental wall movement and thickening. Table 1 shows that up to one month after operation there was a significant decrease in the proportion of segments with normal wall movement. After operation there was a significant increase in the proportion of both dyskinetic and hyperkinetic segments and a significant decrease in the proportion of hypokinetic segments. There was no significant change in the proportion of patients with akinetic segments.

Segmental wall movement scores

Scores for anterior and medial wall movement were significantly less up to one month after operation (table 2). Scores for posterior and lateral wall movement were significantly greater at all postoperative assessments.

Patients with coexistent abnormalities of anterior and posterior wall movement

The frequency of anteromedial hypokinesia or dyskinesia or both was significantly greater up to one month after operation. At six months there was no significant difference. Among these patients, there were parallel and significant increases in the proportion of posterolateral segments that were hyperkinetic.

Segmental wall thickening

There were no significant changes in the qualitative analysis of segmental wall thickening (table 4). A quantitative analysis, however, showed that there was a significant increase in segmental wall thickening during systole in the mid-posterior segment throughout follow up and in the posterobasal segment at six months (table 5).

Postoperative pericardial effusions

At predischage examination five patients had

Table 2 Mean (SD) segmental wall motion score

	Preop	Postoperative values		
		Predischage	1 month	6 months
Anterobasal	1.7 (0.6)	-0.1 (1.2)*	0.2 (1.3)*	0.8 (1.4)†
Mid-anterior	1.5 (0.9)	-0.1 (1.2)*	-0.2 (1.3)*	0.8 (1.4)
Posterobasal	1.9 (0.4)	2.5 (0.6)*	2.7 (0.4)*	2.3 (0.5)†
Mid-posterior	1.8 (0.6)	2.4 (0.7)*	2.6 (0.6)*	2.3 (0.5)†
Lateral basal	1.9 (0.4)	2.5 (0.6)*	2.6 (0.5)*	2.3 (0.5)†
Mid-lateral	1.9 (0.6)	2.4 (0.6)*	2.6 (0.5)*	2.2 (0.7)‡
Medial basal	1.8 (0.5)	0.1 (1.4)*	-0.1 (1.3)*	0.9 (1.3)†
Mid-medial	1.5 (0.8)	0.1 (1.4)*	-0.2 (1.3)*	0.8 (1.4)¶
Apical	1.2 (1.1)	1.0 (1.2)	1.3 (1.1)	1.3 (1.1)

Comparison with preoperative values: * $p < 0.001$, † $p < 0.05$; ‡ $p < 0.01$; § $p < 0.005$, ¶ $p < 0.02$.

Table 3 Number of patients with wall motion abnormalities

	Preop No (%)	Postoperative values		
		Pre-discharge No (%)	1 month No (%)	6 months No (%)
Anteromedial hypo/dyskinesia	11 (30)	24 (77)*	29 (74)*	17 (44)
Posterolateral hyperkinesia	4 (11)	18 (58)†	29 (74)†	13 (34)*

Comparisons with preoperative values *p < 0.05; †p < 0.005, ‡p < 0.001

Table 4 Segmental wall thickening

	Preop No (%)	Postoperative values		
		Pre-discharge No (%)	1 month No (%)	6 months No (%)
Segments studied	324	279	351	342
Normal thickening	250 (77)	206 (74)	288 (82)	290 (85)
Reduced thickening	50 (15)	53 (19)	46 (13)	36 (10)
No thickening	24 (7)	20 (7)	17 (5)	16 (5)

moderate pericardial effusions that persisted at one month in three. All effusions had resolved completely and spontaneously by six months.

ELECTROCARDIOGRAPHIC CHANGES

Three patients developed electrocardiographic changes suggestive of perioperative myocardial infarction. One of these patients, who developed new Q waves in the inferior leads, had a normal echocardiogram and electrocardiogram before operation. After operation he developed paradoxical movement of the anterior and medial walls with normal thickening and hyperkinetic posterior and lateral wall movement with slightly reduced posterior wall thickening. The second patient developed reduced R wave progression in the anterior chest leads after operation. Before operation he had apical akinesia and mid-anterior and mid-medial hypokinesia with

abnormal thickening of these segments. After operation he developed anterior and medial dyskinesia with posterior and lateral hyperkinesia and deterioration in anterior and medial wall thickening. The third patient developed new Q waves in leads V1-V3. He had a normal echocardiogram before operation but developed paradoxical anterior and medial wall movement and hyperkinetic posterior and lateral wall movement with slightly reduced medial wall thickening at predischARGE examination. His echocardiogram reverted to normal by six months.

Discussion

Coronary artery surgery is generally considered to be effective in relieving angina pectoris,^{3,4} and the results from our study substantiate this. Features of exercise induced myocardial ischaemia, exercise duration, and haemodynamic function all improved progressively and significantly during the six month follow up. The increases in heart rate and double product after operation may be explained by the withdrawal of β blockers. Antianginal medication may mask exercise induced myocardial ischaemia but the frequency of both angina and ST depression decreased significantly after operation indicating effective myocardial revascularisation. Because we did not assess graft patency we did not attempt to correlate segmental wall movement and myocardial blood supply.

The effects of myocardial revascularisation on myocardial function and left ventricular wall movement are controversial. Some workers reported small changes or deteriorations in left ventricular function^{8,9} and regional contractility,¹⁰⁻¹² whereas others found improvements in left ventricular performance.⁵⁻⁷ The discrepancy between these results may be partially explained by differences in imaging techniques, in the timing of postoperative assessments,^{2,10} in patency rates for vein grafts,¹³ or in the methods for assessing segmental wall contractility. Some have analysed segmental wall movement by

Table 5 Segmental wall thickening score (mean (SD))

Segments	Preop	Predischarge postop	1 month postop	6 months postop
Anterobasal	1.7 (0.4)	1.7 (0.5)	1.8 (0.4)	1.7 (0.5)
Mid-anterior	1.5 (0.8)	1.4 (0.7)	1.6 (0.6)	1.7 (0.6)
Posterobasal	1.8 (0.4)	1.9 (0.3)	1.9 (0.8)	1.9 (0.2)*
Mid-posterior	1.7 (0.5)	1.8 (0.3)*	1.9 (0.3)*	1.9 (0.3)*
Lateral basal	1.9 (0.4)	1.9 (0.3)	1.9 (0.2)	1.9 (0.2)
Mid-lateral	1.8 (0.5)	1.8 (0.4)	1.9 (0.3)	1.9 (0.4)
Medial basal	1.8 (0.4)	1.7 (0.5)	1.7 (0.5)	1.8 (0.4)
Mid-medial	1.6 (0.6)	1.5 (0.7)	1.6 (0.6)	1.8 (0.4)
Apical	1.3 (0.9)	1.1 (0.9)	1.4 (0.9)	1.5 (0.8)

Comparison with preoperative values *p < 0.05

reference to the visual field of the screen, whereas others used the centre of the left ventricular cavity.¹⁴ It has been suggested that regional wall thickening is more sensitive than regional wall movement for the identification of the extent of the myocardium at risk.¹⁵ For this reason we analysed regional wall movement and thickening separately.

We found that most wall segments were moving abnormally after operation, especially soon after operation and one month postoperatively. The anterior and medial wall segments moved paradoxically and movement of the posterior and lateral wall was exaggerated. These findings are consistent with previous reports.^{10,12} There were no significant abnormalities in left ventricular wall thickening after operation in our patients, but in some patients regional wall thickening, particularly of the posterior wall, was improved. One explanation for this observation is that there was no additional abnormality in segmental wall contractility after coronary artery surgery, but the whole heart moved anteriorly and medially during systole. The mechanism for such segmental wall abnormalities is unclear, but it has been suggested that pericardiotomy may be at least partly responsible.¹⁰ Occult septal myocardial damage has also been proposed as a cause of this movement abnormality.^{10,12,16} A Venturi effect (caused by the high blood viscosity in the grafts) may reduce blood flow in the septal perforating branches,¹⁷ but this should also cause abnormal septal wall thickening, which we did not find in our patients.

The decrease in fractional shortening at one month may be related to the pattern of the movement of the heart during systole. Six months after operation there was no significant difference in fractional shortening and most of the abnormalities of segmental wall movement had also resolved.

Bypass-related myocardial damage or ischaemia sufficient to cause an abnormality in wall movement at rest are unlikely mechanisms for the observed wall movement abnormalities in these patients. Perioperative infarction was rare and haemodynamic function during exercise, the duration of exercise, and inducible ischaemia all generally improved rather than deteriorated after coronary operation. Other studies have also reported a significant improvement in the haemodynamic function of the left ventricle in response to stress after coronary artery operation.^{18,19}

Three of our patients had a perioperative myocardial infarction and all three also developed new abnormalities of wall movement. These were present in most patients soon after operation, and so in isolation they seem to be poor markers of perioperative infarction unless they are accompanied by new abnormalities in wall thickening.²⁰

We conclude that new abnormalities in left ventricular wall movement commonly develop soon after coronary artery surgery, but they usually resolve by six months and do not seem to influence myocardial contractility, exercise performance, or haemodynamic function. Recognition that these changes occur may be clinically useful in the postoperative evaluation of this group of patients.

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Diastolic properties of the normal left ventricle during supine exercise

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SUMMARY Diastolic function in response to dynamic exercise was studied by biplane left ventriculography and by measuring left ventricular pressure with a high fidelity micromanometer tipped catheter at rest and during supine bicycle exercise in nine normal subjects. During exercise there was a fall in end systolic volume, in the time constant of left ventricular isovolumic pressure decay, and in the lowest diastolic pressure. Stroke volume, peak filling rate, mean passive filling rate, and the volume at the lowest diastolic pressure increased. There was an increase in the number of time constants that had elapsed before the lowest diastolic pressure was reached and the slope of the pressure-volume curves during passive filling ($\Delta P/\Delta V$) increased without changes in end diastolic pressure and volume.

These results show that during exercise elastic recoil is enhanced and left ventricular relaxation is faster and more complete. Both phenomena reduce the lowest diastolic filling pressure. The observed increase in chamber stiffness from rest to exercise is probably related to increased resistance of the left ventricular wall caused by higher passive filling rates. The enhanced early diastolic pressure decay during exercise allows stroke volume to increase despite an increase in diastolic viscoelastic resistance and chamber stiffness.

The effects of dynamic exercise on left ventricular function have been analysed in many studies and by various techniques. Attention has focused mainly on the contractile or systolic performance of the left ventricle in experimental¹⁻³ and clinical studies.⁴⁻⁶ Little is known about the diastolic function of the normal heart during exercise. There is general agreement that left ventricular end systolic volume is smaller during exercise than at rest and most investigators have reported an increase in stroke volume during exercise. These data are consistent with an enhanced contractility during exercise, but the role of the Frank-Starling mechanism in the normal heart remains uncertain.^{5,7,8} In most studies, left ventricular end diastolic volume and stroke volume are maintained during exercise despite shortening of the

diastolic filling interval, whereas in pacing-induced tachycardia, both end diastolic volume and stroke volume are reduced.^{9,10} Recently, Higginbotham *et al* showed that at low levels of upright exercise end diastolic volume and stroke volume increase, whereas at maximum levels of exercise end diastolic volume decreases with no further increase in stroke volume.¹¹ These findings suggest that filling is enhanced but it is not known whether and to what extent the passive properties of the left ventricular chamber in diastole are altered during exercise.

In the present study the response of diastolic function to dynamic exercise in normal hearts was evaluated by simultaneously measuring left ventricular pressures and left ventricular volumes during submaximal supine exercise.

Patients and methods

PATIENTS

We studied nine patients (eight men, one woman; aged 35-58, (mean 49)) referred to our hospital for evaluation of chest pain. Five had no cardiovascular abnormalities. Three had minimal coronary artery

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disease (maximal coronary stenosis <50% of the luminal diameter) and one had mitral valve prolapse without mitral regurgitation. They had normal systolic function as defined by resting left ventricular ejection fraction $\geq 57\%$ (the lower limit of normality of our laboratory).¹² The day before catheterisation, all patients had an upright bicycle exercise test and showed normal exercise tolerance (mean work load 132 W) with no ST segment changes and no anginal pain. All patients gave informed consent, and no complications occurred in any of them.

CATHETERISATION AND CINEANGIOGRAPHY

An hour before catheterisation patients were premedicated with 10 mg of oral chlordiazepoxide. Cardiovascular medications were not given for 12 to 24 hours before the study. Left ventricular pressure was measured with a 8F Millar pigtail angiographic micromanometer catheter introduced from the right femoral artery. The pressures were recorded at a paper speed of 250 mm/s (Electronics for Medicine, VR-12) together with the first derivative of pressure (dP/dt) and (dP/dt)/P (fig 1). Before recording at rest and during exercise the micromanometer was calibrated by superimposing the high fidelity pressure tracing on the pressure tracing obtained with a fluid filled catheter. Biplane left ventriculography was performed in the 30° right and 60° left anterior oblique projections at a filming rate of 50 frames per second (Siemens Angioscope). Each angiographic frame had a digital time that corresponded to the time marks on the pressure recordings. A metal sphere of known diameter was filmed in the position of the heart for calibration purposes at the end of the

procedure. The patients held their breath in mid-inspiration during the resting angiogram. If respiration related pressure changes were noted during exercise we selected angiographic beats recorded during mid-inspiration. During cineangiography Valsalva manoeuvres were avoided by instructing the patient, observing the diaphragm, and monitoring right atrial pressure.

EXERCISE PROTOCOL

All patients had upright bicycle exercise testing before catheterisation to determine the exercise tolerance. At catheterisation, pressures were recorded before and after the patient's feet were attached to the pedals of the bicycle. All data at rest were recorded during acquisition of the first angiogram while the patient's feet were raised. After the resting angiogram had been obtained and after a 12–15 minute pause to allow left ventricular pressure to return to the control value, the patient started to exercise at a low level. The work load was increased every two minutes until limiting symptoms occurred or the predicted submaximal heart rate was achieved. At peak exercise pressures were again recorded with simultaneous cineangiography. Coronary arteriography was performed by the Judkins technique at the end of the exercise test.

DATA ANALYSIS

We analysed only sinus beats and excluded postextrasystolic beats. Pressure tracings were digitised for an entire cardiac cycle with an electronic digitiser (Numonics Corporation) interfaced with a computer (PDP 11/34). Pressure and dP/dt values were plotted

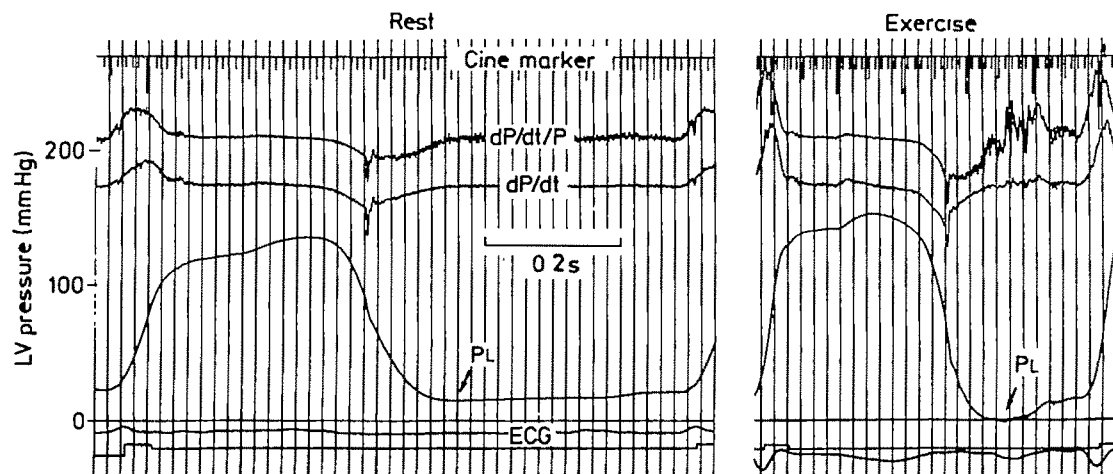


Fig 1 The left ventricular (LV) pressure tracing in the resting state (left) and during exercise (right). The exercise beat had a higher peak systolic pressure but the end diastolic pressure (EDP) was unchanged. The lowest diastolic pressure (P_L) was lower during exercise.

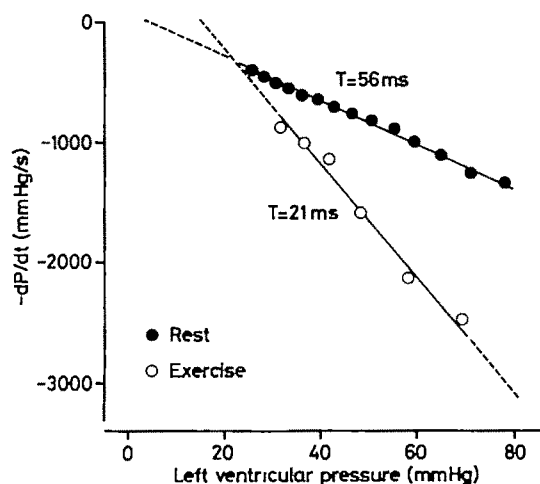


Fig 2 Left ventricular pressure and negative dP/dt coordinates measured during the isovolumic relaxation period. The time constant of relaxation (T) is represented by the negative reciprocal of the slope of the linear regression between pressure and dP/dt coordinates. During exercise T decreased to 21 ms from a control value of 56 ms. This result shows that the speed of relaxation was increased during dynamic exercise.

every 2.5 to 5 ms depending on the heart rate. The time constant for left ventricular pressure decay was calculated as the negative reciprocal of the slope relating left ventricular pressure to dP/dt coordinates between peak negative dP/dt and the time at which pressure had decreased to 5 mm Hg above left ventricular end diastolic pressure (fig 2). To study the completeness of relaxation, we used the technique of Weisfeldt *et al*, which assumes relaxation to be 97% complete at 3.5 time constants after peak negative dP/dt .¹³ We calculated the number of time constants that had elapsed before the time of the lowest diastolic pressure. Left ventricular angiograms for one cardiac cycle were analysed frame by frame by the area-length method.¹⁴ End diastole was defined as the beginning of the rapid rise of left ventricular pressure immediately after the start of the QRS complex. End systole was defined as the angiographically determined point of aortic valve closure.

Left atrial pressure is a major determinant of left ventricular filling.¹⁵ Because left atrial pressure was not measured in the present study, we recorded the pressure at the time at which unopacified blood first entered the ventricle.¹⁶⁻¹⁸ In a previous report we compared the transeptally measured peak left atrial v wave pressure (mitral valve opening pressure) and the left ventricular pressure at the time when

unopacified blood first entered the ventricle in patients with aortic stenosis.¹⁸ The correlation between both pressures was good ($r = 0.911$; $p < 0.001$). The peak v wave pressure was slightly higher (14%) than the pressure when unopacified blood first entered the ventricle. In the present study the pressure when unopacified blood first entered the ventricle correlated significantly ($r = 0.68$, $n = 18$; $p < 0.01$) with end diastolic pressure. Thus the pressure when unopacified blood first entered the ventricle is not the true driving pressure but was used as an index of the left atrial pressure responsible for mitral valve opening.

End diastolic volume, end systolic volume, stroke volume, and ejection fraction were calculated according to standard formulas. Volumes were standardised for body surface area. Early filling volume (volume at the time of the lowest diastolic pressure minus volume at mitral valve opening) was expressed as the percentage of total diastolic filling volume (early filling fraction).¹⁹ Instantaneous diastolic filling rates were calculated every 20 ms after mitral valve opening. To minimise errors caused by random noise in the left ventricular volume-time curve, raw data were filtered with the fifth-grade moving average.^{18,20} Then diastolic filling rate was calculated by a third-degree polynomial function. The highest value occurring early in diastole was termed the peak filling rate. The mean passive filling rate was defined as the volume change from the lowest diastolic pressure to end diastole divided by its time interval. A simple assessment of left ventricular chamber stiffness was calculated as the index ΔP (end diastolic pressure minus the lowest diastolic pressure) divided by ΔV (end diastolic volume minus the volume at the lowest diastolic pressure).²¹

STATISTICAL ANALYSIS

Results are presented as group means (1 SD) in the tables and mean (1 SE) in fig 4. Means at rest and exercise were compared by a paired t test. The level of statistical significance was defined as $p < 0.05$.

Results

Table 1 shows the left ventricular angiographic data and table 2 the pressure data. Leg elevation before exercise was associated with an increase in the left ventricular end diastolic pressure from 10 (3) to 19 (5) mm Hg ($p < 0.001$), in the lowest diastolic pressure from 4 (3) to 9 (4) mm Hg ($p < 0.001$), and in right atrial pressure (six patients) from 3 (1) to 8 (3) mm Hg ($p < 0.001$). The heart rate remained unchanged (from 67 (16) to 69 (17) beats/min). The increase in preload accounts for this increase in filling

Table 1 Angiographic data at rest and during supine exercise in nine patients with normal left ventricular function

Patients	HR	Work	EDV	ESV	SV	EF	PFR	MFR	%V _{PL}	V _{PL}
1 Rest	56	—	98	38	60	61	217	93	13	46
Ex	88	50	111	32	79	71	395	225	43	66
2 Rest	71	—	91	27	64	70	315	140	28	38
Ex	111	50	98	27	71	72	578	231	33	61
3 Rest	71	—	90	31	59	66	361	129	9	41
Ex	107	100	96	31	65	68	398	257	41	63
4 Rest	71	—	99	43	56	57	257	136	13	50
Ex	125	120	104	36	68	65	493	325	29	65
5 Rest	88	—	78	26	52	67	264	175	19	36
Ex	150	100	84	26	58	69	614	363	73	55
6 Rest	57	—	104	43	61	59	258	88	40	60
Ex	103	100	113	43	70	62	372	281	36	68
7 Rest	51	—	87	26	61	70	268	64	24	46
Ex	115	100	80	22	58	73	346	200	45	49
8 Rest	101	—	86	30	56	65	433	281	15	47
Ex	136	60	79	21	58	73	629	420	22	37
9 Rest	55	—	94	34	60	64	316	65	26	59
Ex	130	140	99	24	75	76	788	530	33	48
Rest Mean	69	—	92	33	59	64	299	130	21	47
SD	17	—	8	7	4	5	66	68	10	8
Ex Mean	118	91	96	29	67	70	512	315	40	57
SD	19	31	13	7	8	4	150	108	15	10
p	<0.001	—	NS	<0.05	<0.01	<0.01	<0.01	<0.01	<0.05	<0.05

EDV, left ventricular end diastolic volume index (ml/m²), EF, ejection fraction (%), ESV, left ventricular end systolic volume index (ml/m²), Ex, during exercise, HR, heart rate (beats/min), MFR, mean passive filling rate (ml/s/m²), PFR, peak filling rate (ml/s/m²), %V_{PL} = percentage of early filling volume fraction (%), SV, stroke volume index (ml/m²), V_{PL}, left ventricular volume at the lowest diastolic pressure (ml/m²), work, ergometric work load (W).

pressures. All resting data were measured during the first angiogram and with the patients' legs raised.

ANGIOGRAPHIC DATA

Patients achieved at peak exercise a mean workload of 91 W after 3.7 minutes of exercise. No patient had exercise induced angina. Heart rate increased from

69 to 118 beats/min. Left ventricular end diastolic volume was similar at rest and during exercise, whereas end systolic volume decreased from 33 to 29 ml/m² (p < 0.05). Left ventricular stroke volume and ejection fraction increased significantly during exercise (from 59 to 67 ml/m² (p < 0.01) and from 64 to 70% (p < 0.01) respectively). During exercise the

Table 2 Pressure data at rest and during supine exercise in nine patients with normal left ventricular function

	LVP	EDP	P _L	dP/dt	-dP/dt	RAP	MVOP	T	P _a	Ts at P _L	ΔP/ΔV
1 Rest	95	17	9	963	909	—	9	51.6	-1.4	2.4	0.15
Ex	123	16	6	2031	1567	—	8	35.0	0.1	3.7	0.23
2 Rest	151	21	13	1941	2076	12	15	47.0	-6.2	2.3	0.16
Ex	141	17	2	2434	2626	12	16	28.3	-5.1	3.4	0.42
3 Rest	136	18	9	1466	1808	10	9	38.6	-0.5	2.6	0.18
Ex	193	18	7	2703	2802	10	10	19.2	8.6	3.6	0.29
4 Rest	126	22	14	1490	1399	—	14	55.9	2.1	2.3	0.16
Ex	153	13	2	3204	2500	—	12	23.0	13.4	3.8	0.28
5 Rest	123	14	5	2227	1523	3	11	38.5	-5.5	2.7	0.23
Ex	154	18	3	4477	2811	9	22	18.0	-2.6	3.3	0.52
6 Rest	163	20	10	1369	1856	11	14	52.8	-4.8	3.1	0.22
Ex	173	26	5	2562	2366	12	22	20.7	10.8	4.3	0.47
7 Rest	114	12	4	1474	1375	7	10	53.6	-8.8	2.3	0.18
Ex	131	17	3	3357	2225	9	13	19.6	13.4	4.2	0.44
8 Rest	134	23	5	1992	2296	6	14	26.5	-2.4	3.3	0.40
Ex	151	20	2	3057	2763	6	9	12.7	9.5	4.5	0.42
9 Rest	163	27	16	1282	1541	—	17	58.1	-0.5	2.3	0.32
Ex	171	30	1	4104	3774	—	24	14.5	22.7	5.2	0.54
Rest Mean	134	19	9	1578	1643	8	13	47.0	-3.1	2.6	0.22
SD	23	5	4	398	416	3	3	10.4	3.4	0.4	0.08
Ex Mean	154	19	3	3103	2604	10	15	21.2	7.9	4.0	0.40
SD	22	5	2	792	588	2	6	6.9	2.9	0.6	0.11
p	<0.05	NS	<0.01	<0.001	<0.001	NS	NS	<0.001	<0.01	<0.001	<0.001

dP/dt, peak positive dP/dt (mm Hg/s); EDP, left ventricular end diastolic pressure (mm Hg), LVP, left ventricular peak systolic pressure (mm Hg), -dP/dt, peak negative dP/dt (mm Hg/s), P_L, the lowest diastolic filling pressure (mm Hg), RAP, mean right atrial pressure (mm Hg), ΔP/ΔV, mean passive chamber stiffness index (mm Hg/(ml/m²)); MVOP, mitral valve opening pressure (mm Hg); P_a, asymptote (mm Hg), T, time constant of isovolumetric left ventricular pressure decay (ms), Ts at P_L, the number of Ts elapsed at P_L.

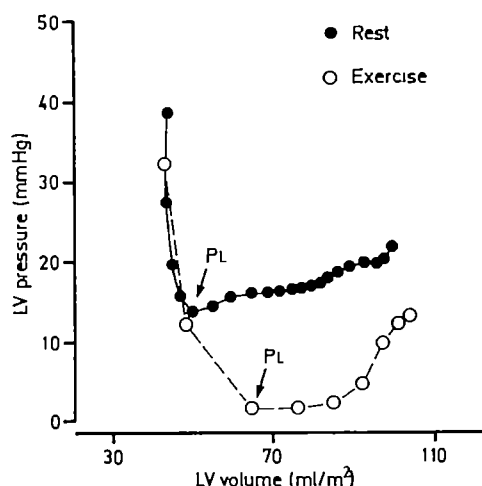


Fig 3 Representative pressure (P)-volume (V) plots in a patient with normal left ventricular function. In the exercise beat the diastolic curve is shifted downward and the slope is steeper than in the resting beat without any change in end diastolic volume. This result suggests a decrease in chamber compliance during exercise

peak filling rate and mean passive filling rate increased markedly (299 to 512 ml/s/m² ($p < 0.01$) and 130 to 315 ml/s/m² ($p < 0.01$) respectively) without a change in mitral valve opening pressure. Early filling fraction and left ventricular volume at the lowest diastolic pressure increased significantly during exercise (21 to 40% ($p < 0.05$) and 47 to 57 ml/m² ($p < 0.05$) respectively).

PRESSURE DATA

Left ventricular peak systolic pressure increased significantly during exercise as did peak positive dP/dt . The lowest diastolic pressure was lower during exercise (9 to 3 mm Hg, $p < 0.01$) than at rest whereas left ventricular end diastolic pressure remained unchanged. Right atrial pressure also remained unchanged. The time constant decreased during exercise (47 to 21 ms ($p < 0.001$)) with an increase in peak negative dP/dt and in the number of time constants that had elapsed before the lowest diastolic pressure was reached (from 2.6 to 4.0, $p < 0.001$). These findings suggest a more complete relaxation during exercise than at rest.

PRESSURE-VOLUME RELATION

The index ΔP (mm Hg)/ ΔV (ml/m²) increased significantly during exercise because the driving pressure increased more for a similar increase in diastolic volume during exercise than it did at rest. Figure 3

shows a representative example of a left ventricular pressure-volume plot. Figure 4 shows the pooled diastolic pressure-volume data of all nine patients. During exercise a decrease in the lowest diastolic pressure was accompanied by an increase in volume.

Both left ventricular end diastolic pressure and volume remained unchanged during exercise. The diastolic pressure-volume curve, however, showed a downward shift and an increase in slope during exercise. These findings suggest an increase in chamber stiffness during exercise. In order to assess the mechanism of increased chamber stiffness during exercise, we analysed the relation between pressure increase (ΔP) and mean passive filling rate (fig 5). There was a significant correlation (coefficient 0.84 ($p < 0.001$)). An increase in passive filling rate is accompanied by an increase in ΔP .

To assess the effect of left ventricular volume at the lowest diastolic pressure on chamber stiffness, we compared left ventricular volume and early filling fraction at the lowest filling pressure with the index ΔP divided by ΔV . There was no significant correlation between left ventricular volume at the lowest diastolic pressure and $\Delta P/\Delta V$, whereas there was a weak but significant correlation ($r = 0.54$, $p < 0.05$) between early filling fraction and $\Delta P/\Delta V$.

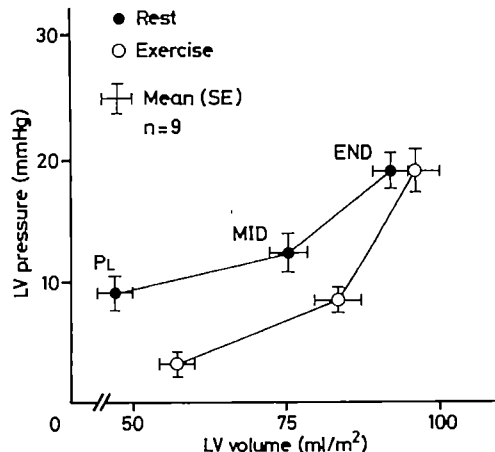


Fig 4 Mean (1 SE) diastolic pressure (P)-volume (V) relations for all nine patients at rest and during exercise. Coordinates of left ventricular (LV) pressure and volume are averages at three reference points: the lowest diastolic pressure (P_L), mid-diastole (MID), and end diastole (END). P_L was lower during exercise than at rest and there was a slight increase in volume. Both end diastolic pressure and volume remained unchanged during exercise. The pressure-volume curve showed a downward shift and an increase in slope during exercise.

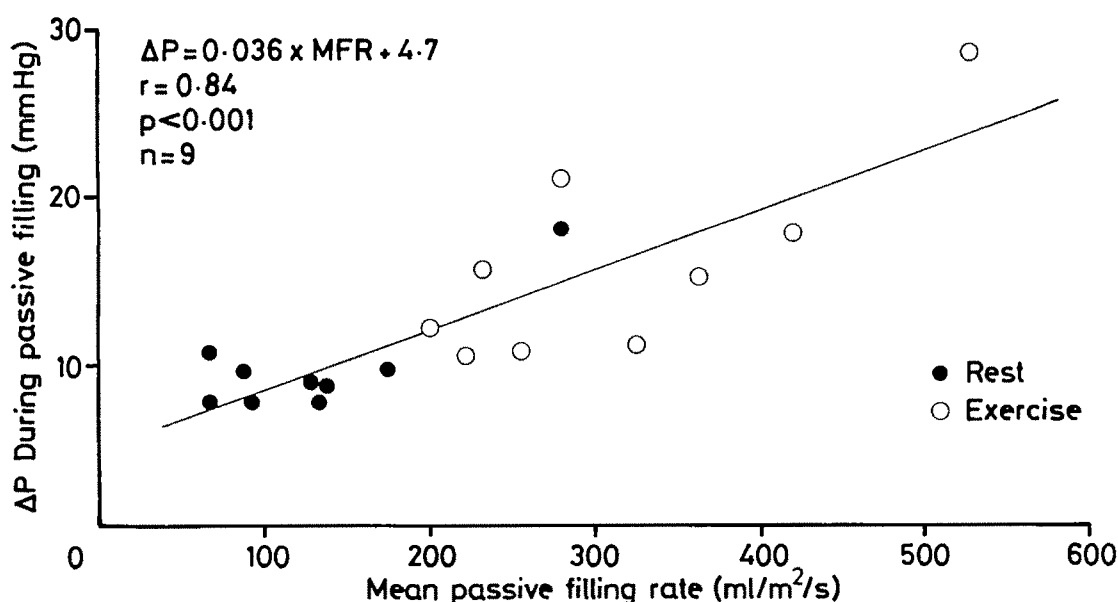


Fig 5 The correlation between the pressure increase (ΔP) and mean passive filling rate (MFR) was good ($r = 0.84$). An increase in filling rate was accompanied by an increase in ΔP .

Discussion

FILLING DYNAMICS AND RELAXATION DURING EXERCISE

In the present study the peak filling rate and early diastolic filling fraction were enhanced during exercise. Two mechanisms must be considered in the interpretation of changes in filling dynamics during exercise in normal subjects.

The first mechanism is the elastic recoil (or diastolic suction) created by systolic contraction. The magnitude of elastic recoil is inversely related to end systolic volume²² or depends on the extent of muscle shortening during systole.²³ In animal studies obstruction of the left ventricular inflow produced negative intraventricular pressures, and at small ventricular volumes the pressure-volume curve fell below the zero pressure line.^{24,25} Ventricular suction augments filling and maintains relatively low filling pressure when heart rate is high during exercise.²² In the present study, end systolic volume decreased slightly ($p < 0.05$) during exercise (a slight decrease in five patients and no change in four patients), while stroke volume increased in eight patients. This condition may be associated with a mild enhancement in elastic recoil.

The second mechanism is related to the enhancement of left ventricular relaxation during exercise. Influences of relaxation on early diastolic filling have been studied in animal models and human

subjects.²⁶⁻²⁸ During exercise relaxation is enhanced both by an increase in sympathetic tone and an increase in heart rate.^{29,30} In the present study during exercise there was a faster, more complete left ventricular relaxation with a decrease in the time constant and an increase in the number of time constants that elapsed before the lowest diastolic pressure was reached.

The left atrial driving pressure after mitral valve opening is another important determinant of filling, especially in the diseased heart.^{15,17,18} In the present study, left atrial pressure was not recorded but the index of mitral valve opening pressure remained unchanged at rest and during exercise. Thus the atrial driving pressure is not a major determinant of left ventricular filling during exercise in the normal left ventricle. Atrioventricular flow depends on the atrioventricular pressure gradient.¹⁵ In the present study, the mitral valve opening pressure was unchanged while the lowest left ventricular filling pressure decreased during exercise, suggesting an increase in the atrioventricular pressure gradient. The maintenance of low diastolic pressures with augmented filling and enhanced relaxation is beneficial during exercise when diastole is considerably shortened.

PASSIVE DIASTOLIC PROPERTIES DURING EXERCISE

During exercise, the diastolic pressure-volume

curves showed a downward shift and an increase in slope (figs 3 and 4). These findings suggest an increase in chamber stiffness during passive diastolic filling. The change in left ventricular chamber stiffness may be attributed to several extrinsic or intrinsic mechanisms. Alterations in right ventricular loading conditions and pericardial constraint seem to be unlikely because the right atrial pressure remained unchanged during exercise. Tomoike *et al* showed that left ventricular end diastolic pressure rose significantly above the control values during strenuous exercise in normal dogs with an open pericardium but end diastolic segment length increased only slightly.³ Also during exercise with regional ischaemia there was no significant elongation of the control segment length even though the left ventricular end diastolic pressure was higher during ischaemia.³

Another mechanism of abnormal diastolic function is related to changes in coronary artery perfusion. An augmented myocardial turgor (erectile effect) may increase chamber stiffness.³¹ Using a Doppler flow probe, Vatner *et al* showed that there was a threefold to fivefold increase in left circumflex coronary blood flow in dogs studied during exercise, but coronary flow per beat remained essentially constant.³² Despite the reported increase in peak coronary flow during early diastole,³² early diastolic filling pressure decreased in our study. Templeton *et al* showed that there was no significant alteration in the viscoelastic properties of the left ventricle when coronary flow was altered within moderate limits.³³ Therefore, the influence of the erectile effect on chamber stiffness during exercise is probably minimal.

Other changes of intrinsic properties include incomplete relaxation, increased viscous resistance, and an altered passive myocardial elasticity. In the present study, however, relaxation was more complete and passive elastic myocardial properties were unlikely to be altered during exercise. The mean passive filling rate increased and viscous resistance probably increased in parallel.^{34,35} The calculated index of chamber stiffness ($\Delta P/\Delta V$) during exercise was almost double that at rest. Pouleur *et al* reported that the viscoelastic forces depended on both the lengthening rate and length of the myocardial fibres at the beginning of passive diastolic filling.³⁴ In our study the index of chamber stiffness was related not only to mean passive filling rate (lengthening rate) but also to the early filling fraction. Because both these values and the volume (length) at the lowest diastolic pressure increased during exercise, it is likely that viscoelastic forces were increased and that this led to an increase in chamber stiffness. Robinson *et al* examined the effect of acute expansion of blood

volume on the cardiac response to maximal upright exercise in six men with minimal cardiac disease.³⁶ An increase in stroke volume and cardiac output (measured by dye dilution) after augmentation of blood volume was accompanied by a slight increase in right atrial pressure at rest. During exercise, the expansion of blood volume induced no increase in stroke volume, but it did cause a considerable increase in right atrial pressure. These findings suggest an effect on the steepest portion of the pressure-volume relation where end diastolic volume would be little affected by an increase in filling pressure.

LIMITATIONS OF THE STUDY

Many methods have been used to assess diastolic compliance;^{37,38} we decided to assess overall diastolic passive filling expressed as the average rate of change in left ventricular volume over the interval from the lowest diastolic pressure to end diastolic pressure. This simple technique avoids many of the assumptions that are implicit in assuming a monoexponential diastolic pressure-volume relation, and avoids the errors of fitting a curve to a few points measured during exercise.^{21,39} The validity of the method we used depends upon the accuracy of the component measurements and the magnitude of ΔP . A fluid filled catheter system overestimates the lowest filling pressure whereas the overshoot with a micromanometer is minimal.⁴⁰ During exercise, however, when pressure changes rapidly, the changes in intraventricular pressure may not accurately reflect changes of intramural pressure because of possible distortion by the fluid coupling between the myocardium and the pressure sensor—that is, the blood in the ventricle. We do not know whether and to what extent the dissociation of intramural and intraventricular fluid dynamics influenced our measurements of diastolic chamber stiffness.

The results of the present analysis of diastolic properties during supine exercise may not be applicable to exercise in the upright position, because in the supine position the pressure-volume relation was already on a steeper portion at rest (because of an increase in preload) than it was in the upright position. During exercise in both positions, however, the gradient of the pressure-volume relation became steeper than under resting conditions.¹¹ Even if there are differences at rest, the change in left ventricular chamber stiffness during exercise is similar in both the supine and upright position.

It is concluded that the decrease in early diastolic filling pressure during exercise in normal subjects is caused by the combined effect of faster and more complete relaxation and increased elastic recoil. An increase in the slope of the passive diastolic pressure-

volume curve is the result of the increased viscoelastic resistance of the left ventricular wall. Enhanced decay of early diastolic pressure permits an increase stroke volume despite augmented diastolic viscous resistance and chamber stiffness during supine submaximal exercise.

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Increase in plasma concentrations of cardiodilatin (amino terminal pro-atrial natriuretic peptide) in cardiac failure and during recumbency

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SUMMARY Plasma concentrations of cardiodilatin, the peptide sequence at the amino terminal of the pro-atrial natriuretic peptide, in 17 normal subjects ranged from 59 to 202 (mean 118 (SEM) (9)) pmol/l. Recumbency increased the mean (SEM) concentration to 160 (13) pmol/l. The plasma concentration of cardiodilatin in 24 patients with congestive cardiac failure was much higher (964 (175) pmol/l) than in the normal subjects. It was highest in those with heart failure in New York Heart Association functional classes III and IV and the concentration correlated both with atrial natriuretic peptide concentrations and left ventricular ejection fraction. Concentrations rose during induced tachycardia in three patients tested. Chromatography showed a single clean peak of plasma cardiodilatin immunoreactivity. It seems that cardiodilatin is a second circulating cardiac peptide that is jointly released with atrial natriuretic peptide by common stimuli.

Other workers have reported that, like atrial natriuretic peptide, three partial cardiodilatin sequences can stimulate renal particulate guanylate cyclase and increase cyclic guanosine monophosphate. The simultaneous release of cardiodilatin in higher circulating concentrations than atrial natriuretic peptide may be relevant to the finding that appropriate concentrations of exogenous atrial natriuretic peptide alone do not produce the full renal effects associated with endogenous peptide release.

Atrial natriuretic peptide is present in the atrium¹⁻³ as part of the 126 amino acid residue prohormone and in the plasma^{4,5} as α -atrial natriuretic peptide, the last 28 amino acids of the carboxy terminal end of the prohormone (fig 1). Its release into the circulation is stimulated by atrial distension caused by plasma volume expansion,^{6,7} and concentrations are raised in congestive cardiac failure⁸⁻¹⁰ and chronic renal failure.^{11,12} Diuresis and natriuresis associated with endogenous release of atrial natriuretic peptide¹³⁻¹⁵ are greater than when similar plasma concentrations are produced by exogenously administered peptide.^{9,16,17} This discrepancy could be explained by the additional renal stimulation induced by the altered cardiac and renal nervous activity resulting from atrial distension¹⁸⁻²⁰. It is also possible that a second

cardiac peptide is released with atrial natriuretic peptide and augments its actions. The term cardiodilatin (fig 1) was initially used to describe a porcine cardiac peptide²¹, it is now used to refer to the amino terminal sequence of the pro-atrial natriuretic peptide.²²⁻²⁴ The suggestion that cardiodilatin is the

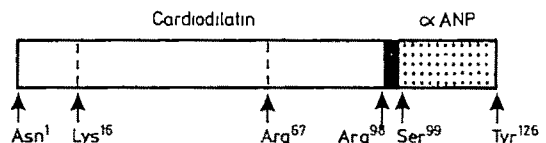


Fig 1 Schematic presentation of the atrial natriuretic peptide prohormone α -Atrial natriuretic peptide is the 28 amino acid residue at the carboxy terminal of the prohormone (Ser⁹⁹-Tyr¹²⁶). Cardiodilatin is the peptide derived from the amino terminal sequence of the prohormone. The Asn¹-Lys¹⁶ sequence (cardiodilatin 1-16) is the fragment used to develop the radioimmunoassay used in this study. The Asn¹-Arg⁶⁷ sequence is cardiodilatin 1-67.

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second cardiac peptide is supported by a recent study that showed that three different amino terminal fragments of the prohormone stimulated renal particulate guanylate cyclase activity and increased cyclic guanosine monophosphate *in vitro*.²⁵

We developed a specific radioimmunoassay for circulating concentrations of cardiodilatin. We used it to study normal subjects during postural change and patients with congestive cardiac failure and during tachycardia.

Patients and methods

CARDIODILATIN RADIOIMMUNOASSAY AND CHROMATOGRAPHY

We used pure synthetic human Asn¹-Lys¹⁶ amino terminal pro-atrial natriuretic peptide (cardiodilatin 1-16 (fig 1) Peninsula Laboratories, Merseyside) to develop the radioimmunoassay.²⁶ Antisera were raised in rabbits and the one used in the assay (final dilution 1:14000) showed 44% cross reactivity with Asn¹-Arg⁶⁷ pro-atrial natriuretic peptide (cardiodilatin 1-67 (fig 1) but no cross reactivity with α -atrial natriuretic peptide. Its cross reactivity with the prohormone or with the complete cardiodilatin 1-98 molecule is not known (synthetic standards were not available). Therefore, the cardiodilatin concentrations measured by the assay, and reported here, are expressed as cardiodilatin 1-16 immunoreactivity equivalents. The radioactive tracer was produced by chloramine T iodination of cardiodilatin 1-16 (sodium iodide ¹²⁵, Amersham IMS 30) and purified by reverse phase high pressure liquid chromatography. Standard curves were constructed with cardiodilatin 1-16.

Plasma samples (50 or 100 μ l) were assayed directly for cardiodilatin immunoreactivity. Assays were incubated at 4°C for four days and separated by dextran coated charcoal (12 mg charcoal:1.2 mg dextran). The detection limit of the assay was 2 fmol/tube and the intra and inter assay coefficients of variation were 7% and 11% respectively. Plasma atrial natriuretic peptide was measured after plasma extraction as described previously.¹²

Plasma cardiodilatin immunoreactivity was characterised by gel permeation chromatography on a column containing G-100 Sephadex (Pharmacia Fine Chemicals, Uppsala, Sweden) and by fast protein liquid chromatography with a peptide reversed phase chromatography high resolution 5/5 (PeprRPC HR5/5) C-18 column (Pharmacia). Samples of neat plasma were loaded onto the gel column. This was eluted with assay buffer (containing 0.2 mol/l sodium chloride) at 1.6 ml per 20 minutes per fraction. With each sample run, dextran blue, cytochrome c, and sodium iodide¹²⁵ were included as

markers of the void volume, molecular size, and total volume. Samples of each fraction were assayed for cardiodilatin immunoreactivity and the elution position was determined.²⁷ Plasma samples were treated with ethanol to precipitate excess protein before fast protein liquid chromatography. After centrifugation, the supernatant was dried in a Savant vacuum centrifuge and the resulting pellet was reconstituted in water (with 0.05% trifluoroacetic acid), passed through a 0.2 μ m filter (Minisart, Sartorius-Instruments, Surrey) and the filtrate was injected onto the column. This was equilibrated with 20% (v/v) acetonitrile in water (each with 0.05% (v/v) trifluoroacetic acid). After injection of a sample the column was eluted with a gradient of acetonitrile from 20% to 40% (v/v) in water over one hour at 1 ml per minute per fraction. Samples of each fraction were assayed for cardiodilatin immunoreactivity. Both columns were calibrated with cardiodilatin 1-67 before and after a series of sample runs.

POSTURE STUDY

We studied 17 normal subjects (14 men, three women, aged 21-42, mean (SD) (28 (5) yr) between 0900 and 1000 after an overnight fast. We collected samples of peripheral venous blood at the start of the study with the subjects sitting and after one hour in the supine position with a 30° passive elevation of the legs. All samples were collected into edetic acid tubes and centrifuged immediately. The plasma was separated and stored at -20°C until assay.

PATIENTS

We studied 24 patients (21 men, three women) aged 23-77 (54 (9)) with stable chronic congestive cardiac failure. The aetiology of the cardiac failure was ischaemic (n = 15) or dilated (n = 9) cardiomyopathy. Three patients were in New York Heart Association functional class I, eight in class II, 10 in class III, and three in class IV. Left ventricular ejection fraction was measured in 21 patients by radionuclide ventriculography²⁸ within 48 hours of blood sampling. The patients were on maintenance drug treatment as follows: diuretics (24), angiotensin converting enzyme inhibitors (10), nitrates (4), digoxin (4), aspirin/anticoagulants (10), β -blockers (1), and amiodarone (2). Samples of peripheral venous blood were taken between 0800 and 0900 after an overnight fast with the patient in the supine position and processed as described above. Samples were also taken from three patients before and during tachycardia, induced by an extra systole and maintained for 10 minutes, in the course of electrophysiological studies for the investigation of tachycardias.

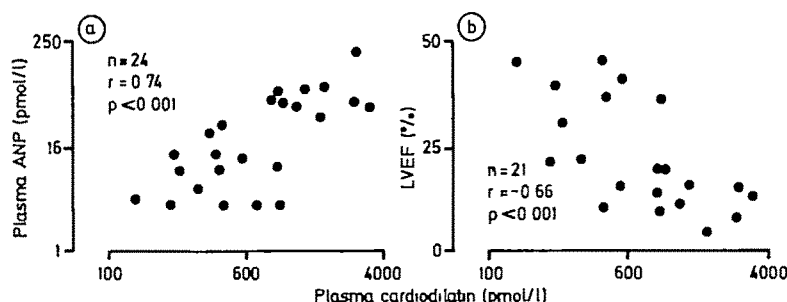


Fig 2 Correlations between cardiodilatin and atrial natriuretic peptide (a) and left ventricular ejection fraction (b) in congestive cardiac failure patients. ANP, atrial natriuretic peptide; LVEF%, left ventricular ejection fraction; r , correlation coefficient. Peptide concentrations are on a log scale.

STATISTICAL ANALYSIS

Concentrations of plasma cardiodilatin (expressed as cardiodilatin 1–16 immunoreactivity equivalents) and atrial natriuretic peptide are given as mean (SEM). We used a two tailed Student's t test for paired or unpaired variables and linear regression analysis of log transformed data (least squares method).

Results

EFFECT OF POSTURE CHANGE

The basal plasma concentrations of cardiodilatin in normal subjects ranged from 59 to 202 pmol/l. Mean (SEM) plasma cardiodilatin increased significantly from 118 (9) pmol/l in the sitting position to 160 (13) pmol/l (range 99–264) when the subject was supine ($p < 0.001$).

PATIENTS WITH CONGESTIVE CARDIAC FAILURE

Plasma concentrations of cardiodilatin were much higher (143–3280 (964 (175)) pmol/l ($p < 0.001$) in patients with congestive cardiac failure. Plasma atrial natriuretic peptide was 34 (9) (4–190) pmol/l. The correlation (fig 2a) between the two peptides was highly significant ($r = 0.74$, $p < 0.001$). Both cardiodilatin (fig 2b) and atrial natriuretic peptide showed strong negative correlations with left ventricular ejection fraction ($r = -0.66$ and -0.67 respectively; $p < 0.001$). Both peptides were significantly higher in patients in New York Heart Association classes III and IV than in classes I and II (cardiodilatin 1340 (280) and 519 (81) pmol/l ($p < 0.02$); atrial natriuretic peptide 54 (15) and 13 (4) pmol/l ($p < 0.02$).

Tachycardia

A mean (SD) rise in heart rate from a basal level of 71 (5) to 180 beats/min was accompanied by a peak

increase in plasma cardiodilatin of 601 (33%), 47 (26%), and 291 (74%) pmol/l from basal values in the three patients studied.

CHROMATOGRAPHY

Gel permeation chromatography (fig 3a and b) of plasma samples from normal volunteers ($n = 8$) and patients with cardiac failure ($n = 4$) showed a single discrete peak of cardiodilatin immunoreactivity with identical elution coefficients of 0.36, eluting earlier than synthetic cardiodilatin 1–67 (elution coefficient of 0.44). The total cardiodilatin immunoreactivity recovered in this peak was 85–105% of the concentrations measured in the original direct plasma assay.

Fast protein liquid chromatography (fig 3c and d) confirmed the presence of a single peak of cardiodilatin immunoreactivity that was identical in normal plasma and in plasma from patients with cardiac failure and eluted at a greater acetonitrile concentration than synthetic cardiodilatin 1–67.

Discussion

Atrial natriuretic peptide and cardiodilatin are the two peptides present at the carboxy and amino terminals of the atrial natriuretic peptide prohormone respectively.^{22–24} Although atrial cells in culture secrete the prohormone,^{29–31} studies on the isolated perfused mammalian heart^{32–34} and intact animals^{33–35} indicate that atrial natriuretic peptide alone and not the prohormone is secreted by the atrium. This was confirmed by chromatography^{45,35} and amino acid sequence analysis of the circulating peptide in man³⁶ and in the rat.^{34,35}

The present data demonstrate that cardiodilatin also circulates in man. In the human atrium cardiodilatin immunoreactivity is present not only as part of the prohormone but also as a separate

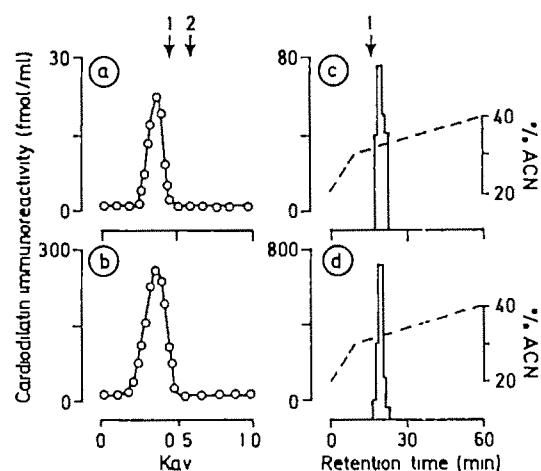


Fig 3 Gel permeation and fast protein liquid chromatographic profiles of plasma coupled with cardiophilin radioimmunoassay. The cardiophilin immunoreactivity for the normal subjects (a) and for patients with cardiac failure (b) co-eluted, with a K_{av} of 0.36 (cardiophilin 1-67 had a K_{av} of 0.44). Fast protein liquid chromatography also indicated that cardiophilin immunoreactivity was similar in the normal subjects (c) and the patients with cardiac failure (d). Cardiophilin eluted later than cardiophilin 1-67. 1, cardiophilin 1-67; 2, horse heart cytochrome c; ACN, acetonitrile.

molecular form that lacks atrial natriuretic peptide immunoreactivity and represents the cleaved amino terminal portion of the prohormone.²⁶ Atrial and plasma cardiophilin immunoreactivity are chromatographically identical and correspond to a smaller and less hydrophobic molecule than pro-atrial natriuretic peptide but larger and more hydrophobic than cardiophilin 1-67. Therefore the Arg⁶⁷ residue of the prohormone (fig 1) is presumably not a site for proteolysis as was previously suggested.²³ Instead, the Arg⁶⁶-Ser⁶⁹ bond seems the most likely cleavage site, simultaneously generating atrial natriuretic peptide^{31,34} and cardiophilin, with the latter containing the entire amino-terminal sequence of the prohormone. Preliminary evidence of coeluting cardiophilin immunoreactive peaks, on chromatography, detected by the present antiserum and by an antiserum raised to the sequence lys⁸⁷-arg⁹⁸ of the prohormone supports this claim (L Meleagros *et al*, unpublished observations).

A second, circulating, cardiac peptide derived from the atrial natriuretic peptide prohormone would be expected to show a similar pattern of release as atrial natriuretic peptide itself. Atrial distension *in vitro*^{32,33} and *in vivo*^{6,7,33} is a recognised stimulus for such release. We found that in normal subjects a supine posture with passive leg elevation increased

plasma cardiophilin. This stimulus is also known to increase atrial natriuretic peptide^{14,37,38} and was attributed to increased intrathoracic blood volume causing atrial distension.

Abnormal atrial distension in congestive cardiac failure was also associated with raised concentrations of atrial natriuretic peptide.⁸⁻¹⁰ The present study shows that plasma cardiophilin was also greatly increased and correlated with atrial natriuretic peptide in patients with congestive cardiac failure. The relations between atrial natriuretic peptide and left ventricular ejection fraction^{8,9} and New York Heart Association functional class^{9,40} were confirmed in our study. We also found that cardiophilin was significantly related to both these variables. Because cardiophilin, unlike atrial natriuretic peptide, does not require an initial laborious extraction step,^{5-15,37} direct assay of plasma cardiophilin may be a useful index of disease severity and possibly of the chronic response to treatment in congestive cardiac failure. Supraventricular tachycardia increases atrial pressure and circulating atrial natriuretic peptide.⁴¹ Similarly, in the present study, tachycardia was associated with a rise in plasma cardiophilin.

Thus the evidence suggests that two cardiac peptides, atrial natriuretic peptide and cardiophilin, behave similarly both during physiological atrial distension and pathological atrial distension. Cardiophilin circulates as a single molecular form, perhaps containing the entire amino terminal sequence of the pro-atrial natriuretic peptide. An amino terminal fragment of the prohormone in the rat had a longer plasma half life⁴² and thus may be the reason why we found higher concentrations of cardiophilin than atrial natriuretic peptide.

Atrial natriuretic peptide was first recognised as a physiological regulator of sodium and water balance when the correlation between changes in its plasma concentrations and alterations in plasma volume was identified.⁵⁻⁸ The present data show the same relation between cardiophilin and sodium and water balance. There is still uncertainty about why a modest rise in endogenous¹³⁻¹⁵ plasma atrial natriuretic peptide has a much greater effect on the kidney than similar concentrations achieved by exogenous infusion.¹⁶ Plasma concentrations need to be at least twice as high^{9,17} to mimic the renal effects associated with endogenously released atrial natriuretic peptide. Other factors that are independent of atrial natriuretic peptide could influence renal function in physiological circumstances but not during exogenous peptide infusions. Certainly, cardiac denervation abolishes the diuresis and natriuresis induced by stretching the atrium.^{18,19} This observation, however, does not diminish the role that atrial natriuretic peptide may have in the regulation of renal function.

This is because atrial stretching in these studies^{18,19} probably did not continue long enough¹⁶ for the actions of atrial natriuretic peptide to become manifest. Cardiac denervation abolishes the inhibitory effect of vagal afferent stimulation upon renal sympathetic tone,²⁰ and this may have resulted in the persistence of renal vasoconstriction that could not be overridden by the actions of atrial natriuretic peptide. In one study no renal effects were observed after atrial stretch that caused a 400% increase in plasma atrial natriuretic peptide, but an increase in plasma concentration of almost 1500% after exogenous peptide infusion was also ineffective.¹⁸ Thus either the experimental period was too short, or the dog model, which was used exclusively in these experiments,^{18,19} may be unsuitable. The finding that atrial natriuretic peptide blockade by monoclonal antibodies abolishes the renal effects of atrial distension,^{4,5} further emphasises the role of this peptide.

It seems likely that the renal changes that follow atrial stretch are the result of cardiac nerve stimulation and the actions of atrial natriuretic peptide. In addition to these, a second cardiac peptide may also influence renal function. It is therefore of interest that three different amino terminal fragments of pro-atrial natriuretic peptide, which together make up almost the entire cardiodilatin sequence, were recently reported to be nearly as potent as the atrial natriuretic peptide itself in stimulating particulate guanylate cyclase activity and increasing cyclic guanosine monophosphate in renal tissues in vitro.²⁵ This finding together with the evidence presented in this paper, of concomitant release of atrial natriuretic peptide and cardiodilatin, suggest a possible role for this second cardiac peptide in potentiating the effects of endogenous atrial natriuretic peptide and may help to explain why exogenous peptide does not have the same renal effects as endogenous peptide.

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Failure of dopexamine to maintain haemodynamic improvement in patients with chronic heart failure

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SUMMARY Ten patients with chronic heart failure were given a continuous infusion of dopexamine after an initial stage of dose titration. On the dose selected the cardiac index initially rose by 56%, as a result of an increase in both heart rate and stroke volume index. Systemic vascular resistance fell by 34% and the mean arterial pressure did not change. Within 18 hours of the start of the continuous infusion, however, all the variables except heart rate had returned to preinfusion values. Nine of the 10 patients were withdrawn from the 48 hour study, six because of haemodynamic deterioration and two because of side effects.

If the premature loss of therapeutic effect reflects an intrinsic property of this agent, dopexamine may be of limited clinical value.

Although dopamine may be of value in the management of chronic heart failure,¹ vasoconstriction, which results from α adrenoceptor stimulation, has limited its use.² Dopexamine is a new analogue of dopamine and like the parent compound it must be given intravenously. Although it is as potent as dopamine in increasing renal blood flow, the two agents have different systemic effects.³ Because dopexamine is a potent β_2 adrenoceptor agonist with no action on α adrenoceptors it produces systemic vasodilatation.⁴ And although it does not have appreciable β_1 adrenoceptor activity there is increasing evidence that dopexamine does have inotropic properties,⁵ perhaps through an action on myocardial β_2 receptors.⁶

Inotropes and vasodilators are used to treat resistant heart failure and both clinical and physiological evidence support their use in combination.⁷ Because dopexamine is a vasodilator with inotropic properties it may have a role in the management of such patients.

The acute haemodynamic response to dopexamine in chronic heart failure has previously been described.^{8,9} Intravenous administration reduces the systemic vascular resistance and increases cardiac output; mean arterial pressure does not change. Furthermore, this occurs without a significant

change in myocardial oxygen consumption or metabolic function.⁸

These studies, however, described only the immediate response to a range of dopexamine doses, with each individual dose being administered for 10 or 15 minutes. For dopexamine to be of clinical value a sustained haemodynamic response is required and the present study was designed to examine the response to continuous infusion.

Patients and methods

PATIENTS

We studied 10 patients with chronic heart failure (seven men and three women aged 51 to 69 years (mean of 60)). All were breathless at rest or on minimal effort (New York Heart Association class III or IV), and their symptoms had become worse one week to six months before admission. The cause of heart failure was ischaemic in seven patients and a dilated cardiomyopathy in three. Two patients were diabetic, one treated with an oral hypoglycaemic agent and the other insulin. One patient was in atrial fibrillation.

All were taking a loop diuretic. This was frusemide (80-1000 mg daily, mean of 350 mg) in nine and bumetanide (10 mg daily) in one. Four patients were taking digoxin and three were already taking oral vasodilators (captopril, enalapril, and flosequinan).

Before admission breathlessness had worsened in all patients, but they were judged to be clinically and haemodynamically stable before entry into the study.

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In each case their bodyweight and medication were unchanged for at least 48 hours before the start of the study. Informed consent was obtained from all patients and the protocol was approved by the hospital ethics committee.

METHODS

A balloon-tipped thermodilution catheter (Mansfield Scientific Inc) was inserted via a subclavian vein and positioned in the pulmonary artery. Pressures were measured by a fluid filled system with the patient supine and the breath held in expiration. Cardiac output was measured by thermodilution with a cardiac output computer (American Edwards Laboratory Model 9520A). The mean of three separate readings was taken. Heart rate and rhythm were monitored continuously throughout the study and arterial blood pressure was measured by a sphygmomanometer and standard adult cuff.

Heart rate, blood pressure, cardiac output (CO), and pulmonary artery pressure (PAP) were recorded in all patients. A consistent pulmonary capillary wedge pressure could not be measured in two patients and so diastolic pulmonary artery pressure, rather than wedge pressure, was used as a measure of left ventricular end diastolic pressure in these patients. This is why we used a modified formula for the calculation of pulmonary vascular resistance (PVR) with diastolic pulmonary artery pressure being used instead of pulmonary capillary wedge pressure. The formula was as follows:

$$PVR = \frac{(\text{Mean PAP} - \text{diastolic PAP})}{CO} \times 80 \text{ dyn.s.cm}^{-5}$$

Because right atrial pressure was only recorded during catheter insertion systemic vascular resistance (SVR) was calculated as follows:

$$SVR = \frac{\text{mean arterial pressure}}{CO} \times 80 \text{ dyn.s.cm}^{-5}$$

Cardiac index, stroke volume index, mean arterial pressure, and mean pulmonary artery pressure were calculated according to standard formulas.

DRUG ADMINISTRATION

Each patient was given a range of dopexamine doses and the haemodynamic response to each was assessed (stage I). The dose that produced the best haemodynamic improvement was then continued for a further 48 hours (stage II). Throughout the period of study patients continued on their regular medication.

STAGE I

After two sets of baseline readings had been taken at 15 minute intervals dopexamine (diluted in 500 ml of 5% dextrose) was infused at an initial rate of 1 µg/kg/

min. The dose was subsequently increased to 2, 4, and 6 µg/kg/min, with each dose being maintained for 15 minutes. Haemodynamic variables were measured at the end of each 15 minute period before the next dose was given.

STAGE II

The optimal dose was then continued for 24 hours, with haemodynamic monitoring every three hours except when the patient was sleeping. After 24 hours the infusion was stopped and readings were taken every 30 minutes until they became stable. The infusion was then restarted at the previous dose for a further 24 hour period with measurements every three hours as before. At the end of the infusion readings were repeated every 30 minutes until they again became stable.

During the 48 hour period the rate of infusion was adjusted at the discretion of the clinician. If, however, patients needed additional treatment or had side effects they were withdrawn from the study.

ANALYSIS OF RESULTS

Results are given as mean (SE). We used analysis of variance by the least squares method to assess the significance of the treatment effect.¹⁰

Results

STAGE I

Table 1 shows the results of dose titration compared with the mean preinfusion values. One patient was excluded from this analysis because he did not receive 6 µg/kg/min of dopexamine, a satisfactory response having been obtained at the lower doses. At a dose of 6 µg/kg/min the cardiac index rose from 1.8 (0.2) to 2.8 (0.3) l/min/m², an increase of 57% ($p < 0.001$). This resulted from increases in heart rate from 97 (6) to 114 (5) beats/min (18%, $p < 0.001$) and stroke volume index from 19 (2) to 25 (2) ml/m² (32%, $p < 0.001$). Mean systemic and pulmonary artery pressures were unchanged. Systemic vascular resistance fell by 34% from 2363 (260) to 1549 (298) dyn.s.cm⁻⁵ ($p < 0.001$) and the pulmonary vascular resistance from 233 (39) to 159 (29) dyn.s.cm⁻⁵ (32%, $p < 0.001$). Pulmonary capillary wedge pressure (diastolic pulmonary artery pressure) did not alter.

STAGE II

All patients then entered the second stage. Four were started on 6 µg/kg/min, five on 4 µg/kg/min, and one on 2 µg/kg/min. In two patients the dose was subsequently altered because of deteriorating symptoms.

Only one of the 10 patients completed the study. Three were withdrawn because of worsening dyspnoea, two as a result of symptomatic hypotension,

Table 1 Short term haemodynamic response (mean (1SE)) to four doses of dopexamine in nine patients

	Control*	Dopexamine dose				p†
		1 µg/kg/min	2 µg/kg/min	4 µg/kg/min	6 µg/kg/min	
HR (beats/min)	97 (6)	104 (6)†	107 (5)	111 (5)	114 (5)	<0.001
CI (l/min/m ²)	1.8 (0.2)	2.1 (0.2)†	2.3 (0.2)	2.6 (0.2)	2.8 (0.3)	<0.001
MAP (mm Hg)	82 (3)	84 (4)	85 (4)	82 (4)	80 (5)	NS
SVI (ml/beat/m ²)	19 (2)	21 (2)	22 (2)	24 (3)†	25 (2)	<0.001
SVR (dyn.s.cm ⁻⁵)	2363 (260)	2105 (282)†	2014 (325)	1706 (269)	1549 (298)	<0.001
PAM (mm Hg)	41 (3)	42 (3)	43 (3)	42 (3)	42 (3)	NS
PVR (dyn.s.cm ⁻⁵)	233 (39)	204 (35)	206 (31)	186 (34)†	159 (29)	<0.001
PCWP/DPAP	31 (2)	33 (3)	32 (3)	31 (5)	31 (5)	NS

*Control values are the mean of two baseline readings.

†Lowest dopexamine dose that produces a significant treatment effect

‡Statistical significance of treatment effect

HR, heart rate; CI, cardiac index; MAP, mean arterial pressure; SVI, stroke volume index; SVR, systemic vascular resistance; PAM, pulmonary artery mean; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; DPAP, diastolic pulmonary artery pressure.

and one because of failure to respond during either stage. Two patients were withdrawn because of possible side effects and one asked for the study to be stopped because of increasing malaise in association with a falling cardiac index. Two patients were withdrawn from the study within the first six hours and the remainder between 15 and 24 hours.

Table 2 shows serial measurements of haemodynamic variables in the eight patients in whom the infusion continued for at least 15 hours. The mean preinfusion values are compared with those in stage I after three hours, and when they were repeated at 15–18 hours on the same dose of dopexamine.

On the dose selected, cardiac index initially rose by 56% and stroke volume index by 35%, and although the treatment effect was still significant after three hours, both variables had returned to the control values by 18 hours. A similar pattern was seen for systemic and pulmonary vascular resistance, which fell by 34% and 33% respectively. Again a significant reduction was still present after three hours but both returned to control values within 18 hours.

By 18 hours only heart rate remained significantly different from control values. Pulmonary capillary wedge pressure (diastolic pulmonary artery pres-

sure), mean arterial pressure, and mean pulmonary artery pressure did not alter during the infusion.

Figure 1 shows the change in cardiac index during the infusion in all 10 patients. For reasons of clarity, we did not include two measurements that were taken after the dose of dopexamine was changed. During the period of infusion cardiac index declined in all 10 patients.

Figure 2 shows the results obtained in the only patient who completed the protocol. After an initial response the cardiac index fell with time to approach the preinfusion value after 24 hours. Restarting the infusion after one hour resulted in partial restoration of the initial treatment effect which again declined with time. When the infusion was abruptly stopped after each 24 hour period the cardiac index fell to below its preinfusion value.

UNWANTED EFFECTS

In one patient ventricular fibrillation developed after 21 hours on 6 µg/kg/min dopexamine. There had been no preceding history of arrhythmias and after resuscitation the serum potassium was 3.6 mmol/l. Ventricular fibrillation did not recur after the infusion was stopped and the pulmonary artery

Table 2 Haemodynamic response in eight patients during dose titration (stage I) and continuous infusion compared with preinfusion values (mean (1SE))

	Control†	Stage I	3 h	15–18 h
HR (beats/min)	95 (6)	108 (6)***	105 (5)***	107 (5)***
CI (l/min/m ²)	1.8 (0.2)	2.8 (0.3)***	2.6 (0.3)***	1.9 (0.2)
MAP (mm Hg)	83 (4)	80 (6)	82 (6)	79 (6)
SVI (ml/beat/m ²)	20 (3)	27 (3)***	25 (3)***	19 (3)
SVR (dyn.s.cm ⁻⁵)	2352 (277)	1556 (312)**	1826 (451)**	2254 (434)
PAM (mm Hg)	40 (3)	38 (4)	39 (3)	41 (1)
PVR (dyn.s.cm ⁻⁵)	214 (48)	144 (35)*	155 (46)*	194 (34)
PCWP/DPAP (mm-Hg)	31 (3)	28 (3)	29.5 (3)	31 (1)

*p < 0.05; **p < 0.01; ***p < 0.001.

†Mean of two baseline readings.

See table 1 for abbreviations.

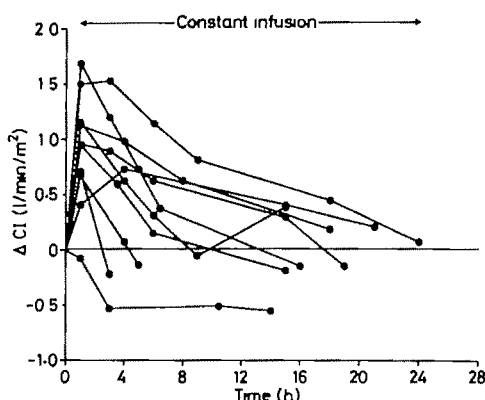


Fig 1 Change in cardiac index (Δ CI) in 10 patients during dose titration and constant infusion of dopexamine.

catheter was removed. This patient was also taking flosequinan and an interaction between the two agents cannot be excluded. In the patient who completed the study ventricular tachycardia developed four hours after the infusion had been stopped. No important arrhythmias were seen in the other eight patients.

In the insulin dependent diabetic, glycaemic control became worse but ketosis did not develop. Over the preceding 48 hours his blood sugar had ranged from 6 to 13 mmol/l. After 15 hours on 4 μ g/kg/min dopexamine his blood sugar had risen to 23 mmol/l and he experienced intense nausea. Over this period he had received 35 g of dextrose by infusion (for thermolulution and dopexamine administration) and he was also confined to bed. Both factors may have contributed to the development of hyperglycaemia, but β_2 adrenoceptor stimulation by dopexamine could also have been responsible. Glycaemic control was not assessed in the other diabetic patient because breathlessness led to the infusion being stopped after three hours.

In four of the 10 patients nausea developed during the infusion and caused vomiting in one patient. No other side effects were reported.

Discussion

This study confirms the impressive acute haemodynamic response to dopexamine that has previously been reported.^{8,9} Short term infusion increased the cardiac index, heart rate, and stroke volume index; reduced systemic and pulmonary vascular resistance; and did not change mean arterial pressure. When Dawson *et al* used a similar dose range the mean rise in the cardiac index was 132%⁸ compared with 57% in the present study. The difference in magnitude of

response may reflect differing severities of heart failure in the two patient groups.¹¹ They also reported a slight fall in the left ventricular end diastolic pressure which was not seen in our patients.

During the second stage of our study there was a progressive decline in treatment effect with time. After 18 hours only heart rate remained significantly different from the control value. In the one patient who completed the study, the initial response was partly restored when the infusion was stopped for one hour but there was a further decline with time.

Haemodynamic deterioration resulted in withdrawal of six of the 10 patients, two further patients being withdrawn because of possible side effects. Nausea in four patients was probably caused by stimulation of dopamine receptors in the chemoreceptor trigger zone.³

The important feature of this study was the rapid decline in therapeutic effect with time. The clinical state of the patients was considered to be stable before they entered the study and cannot explain this finding. Downregulation of adrenoceptors follows prolonged exposure to agonists^{12,13} but in patients with heart failure receiving dobutamine this is only apparent after 72 hours.^{14,15}

It is unwise, however, to draw direct comparisons with previous studies and the findings of the present study should be interpreted with caution. The number of patients was small and all had severe chronic heart failure. If adrenoceptor downregulation is indeed the mechanism responsible, premature downregulation may result from reduced adrenoceptor number¹⁶ and sensitivity,¹⁷ which reflect the severity of myocardial dysfunction. Furthermore, the dopexamine dose, level of response obtained, and the concomitant use of oral vasodilators^{18,19} may all affect the rate of downregulation. Differences in

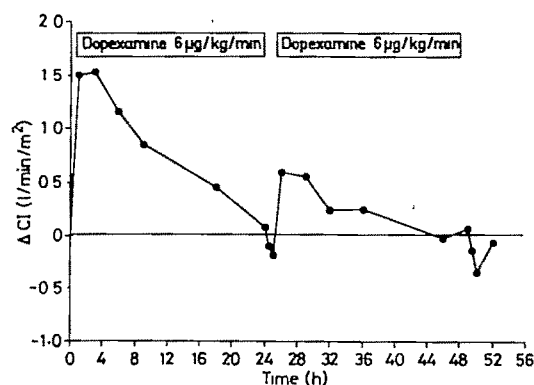


Fig 2 Change in cardiac index (Δ CI) during dopexamine infusion in the one patient who completed the study. The two 24 hour periods are separated by a break of one hour.

patient selection may help to explain the apparently contradictory findings of Colardyn *et al.*,²⁰ who did not find tolerance to dopexamine in a study similar to the present one.

Finally, although chronic heart failure is the model frequently chosen, agents such as dopexamine are used primarily in the setting of acute heart failure where the adrenoceptors are likely to be normal.

Clearly further studies are required, both in acute and chronic heart failure, and these should include direct comparison with existing agents. Until, however, the question of tolerance has been resolved dopexamine cannot be recommended for the treatment of chronic heart failure.

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Doppler assessment of the interventricular pressure drop in patients with ventricular septal defects

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SUMMARY Doppler ultrasound was used to assess the pressure drop between the ventricles in 109 infants and children (61 < two years old) with a ventricular septal defect who underwent cardiac catheterisation. The pressure in both ventricles was measured at catheterisation in 103 patients either simultaneously through two catheters (41) or with a single catheter withdrawn across the septum or removed from one ventricle to the other (62). When pressure was measured simultaneously with two catheters (41 patients) the peak to peak and instantaneous gradients showed a maximum difference of 20 mm Hg with levels within 10 mm Hg of each other in 36. Comparison of the difference in the gradients with the average of the measurements demonstrated a tendency for Doppler to underestimate the difference when it was high (> 50 mm Hg) and overestimate it when it was low. A Doppler estimate of a low pressure difference between the ventricles indicates pulmonary arterial hypertension and a high one low pulmonary artery pressure, but in the intermediate group Doppler is as yet not sufficiently sensitive to allow selection of those patients who require further investigation and possible operation. Doppler ultrasound was found to be a sensitive method of detecting a very small ventricular septal defect. Thus although Doppler is a very useful means of assessing and following patients with a ventricular septal defect, further studies are required to determine its exact place in clinical practice.

In the assessment of the patient with a ventricular septal defect echocardiography simplifies the diagnosis, localisation, and measurement of the size of the defect and can provide information of prognostic value.¹ Accurate knowledge of its haemodynamic effects, however, cannot be obtained from imaging ultrasound and the decision on the need for surgical closure is still based largely upon cardiac catheterisation, with direct measurement of the pulmonary pressure, blood flow, and vascular resistance. Doppler ultrasound now provides a non-invasive means for obtaining physiological information and in those with a ventricular septal defect can potentially provide an estimate of the pulmonary pressure and flow.

Several different methods of measuring the pulmonary artery pressure with Doppler have been reported²⁻⁴; one of the most simple is the use of the

Bernoulli formula⁵ to measure the pressure drop from the left to the right ventricle.^{2,6} Theoretically, subtraction of this value from the systolic blood pressure will provide an estimate of the right ventricular pressure and thus of the pulmonary artery systolic pressure. There are potential inaccuracies in this technique, in particular possible overestimation of right ventricular pressure because of failure to align the beam with the flow jet, or underestimation because of differences between peak to peak and instantaneous gradients. While the initial reported study did indeed show a tendency to underestimate the pressure gradient when it was high (and thus to overestimate right ventricular pressure),² two subsequent ones did not confirm this.^{6,7} These were studies of 52,² 28,⁶ and 38⁷ patients who had catheter studies. Simultaneous right and left ventricular pressures were measured in only 21 and it has not been shown whether there is a significant difference between the peak to peak and instantaneous gradients across a ventricular septal defect. Furthermore, only a total of 20 patients under two years were included in these studies and it is in this age range that the right

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ventricular pressure is likely to be high and accurate assessment of pulmonary artery pressure is most important to decide whether surgical closure is needed.

Further consideration of the technique is justified. Most critical is the accurate measurement of the pressure drop between the ventricles which we assessed in 109 patients with ventricular septal defect undergoing cardiac catheterisation; in 41 both ventricular pressures were measured simultaneously.

Patients and methods

We studied 109 patients aged 10 days to 17 years (mean 3 years 6 months); 61 were less than two years old, including 46 who were less than one year old. All underwent cardiac catheterisation, ventricular pressures being measured through fluid filled catheters attached to strain gauge transducers. In six the left ventricle could not be entered via the left atrium or through the ventricular septal defect and the physician decided not to attempt an arterial approach. The remaining 103 had situs solitus with atrioventricular and ventriculoarterial concordance; seven had multiple defects, nine a ductus arteriosus, 12 aortic valve disease, seven previous coarctation repair, four a pulmonary artery band, two an atrial septal defect, two mitral regurgitation, one significant pulmonary regurgitation, and two peripheral pulmonary artery stenosis. None had significant pulmonary stenosis or an atrioventricular canal. In these 103, ventricular pressures were measured either simultaneously through two catheters (41) or consecutively through a single catheter removed from one ventricle to the other or withdrawn across the ventricular septal defect from the left to right ventricle. The peak to peak pressure difference was measured in all and the instantaneous maximum gradient was measured in the 41 in whom simultaneous ventricular pressures were recorded.

In 85 patients the Doppler studies were performed at the time of catheterisation close to the time that withdrawal pressure was measured or simultaneously with pressure measurements in the 41 in whom the dual catheter system was used; in the others the study was performed within 24 hours of catheterisation. Doppler studies were performed with either a non-imaging continuous wave transducer with an Alfred Velocimeter interfaced to a Doptek spectrum analyser or with a Vingmed CFM 700 system with imaging and colour flow mapping. A cross sectional echocardiogram was performed to demonstrate the position of the septum and, in most patients, the site of the ventricular septal defect. Since the image gives only a guide to the optimal position and angulation for recording maximum

velocity of flow, the entire left parasternal edge and the subxiphoid position were explored and the position and angulation of the probe were adjusted to obtain the maximum velocity signal.

The maximum frequency shift was measured from the Doppler signal; from which the maximum velocity in m/s (V) was derived and the pressure drop in mm Hg (P) estimated from the modified Bernoulli formula, $P = 4V^2$.

The Doppler estimate of the pressure drop was then compared with the following measured pressure differences: peak to peak in the total population of 103 patients; peak to peak in the 41 in whom simultaneous ventricular pressures were measured; and instantaneous maximum gradient in these 41 patients. In addition, in these 41 subjects the measured peak to peak and instantaneous maximum gradients were compared.

Results

MEASUREMENT OF THE PRESSURE GRADIENT

Peak to peak gradients (103 patients) ranged from 0 to 135 mm Hg and instantaneous ones (41 patients) from 0 to 155 mm Hg. The mean difference between the instantaneous maximum and peak to peak gradients (41 patients) was 5.9 mm Hg and it was greater than 10 mm Hg in only five of the 41 patients: 12 mm Hg (76 v 64), 15 mm Hg (92 v 77), 15 mm Hg (25 v 10), 16 mm Hg (58 v 42), and 20 mm Hg (155 v 135).

DOPPLER STUDIES

The maximum velocity flow signal was most frequently obtained from the mid to low left parasternal edge but on occasions it was found with the transducer in a more lateral or a subxiphoid position. The signal rose to its maximum velocity in approximately mid-systole, fell in late systole to its lowest level just after aortic valve closure, and usually, but not always, continued with low velocity flow through diastole (figs 1 and 2). In some instances an early to mid-diastolic velocity increase seemed to be caused by the superimposition of mitral valve flow. The signal was positive indicating flow towards the transducer in all but two patients, who had small muscular defects with the jet emerging from the septum at such an angle that it was directed away from the transducer. With a high velocity jet and a small defect it was not always possible to obtain a complete spectral envelope with a single transducer angulation; in some instances a slight alteration of the position of the transducer showed both the upstroke and downstroke (fig 3), though not necessarily simultaneously, and this permitted the maximum velocity to be measured. It was often important to increase the level

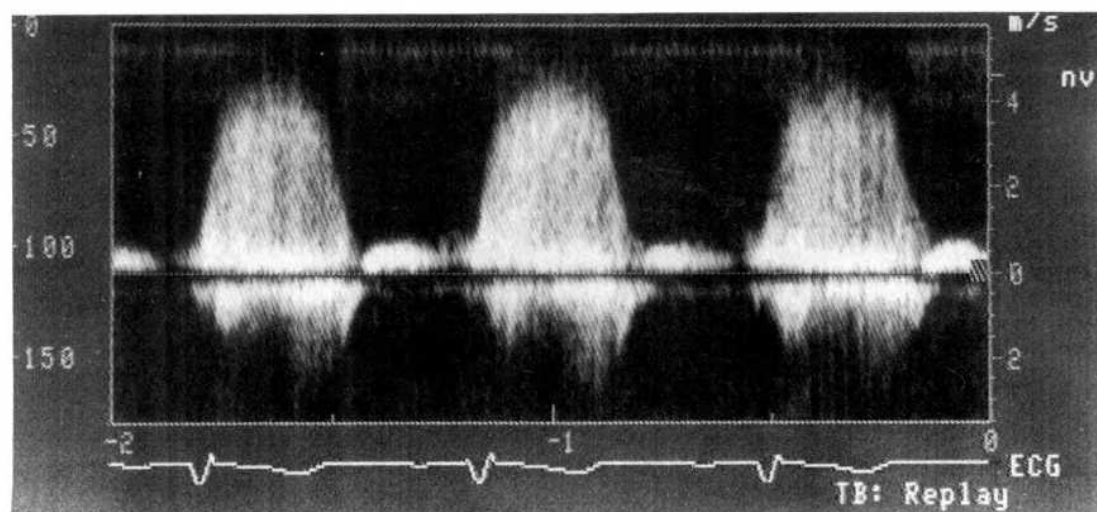


Fig 1 Spectral signal of flow through a ventricular septal defect in a patient with low pulmonary artery pressure and thus a large pressure difference between the ventricles. The maximum velocity of 4.25 m/s is equivalent to a pressure difference of 72 mm Hg.

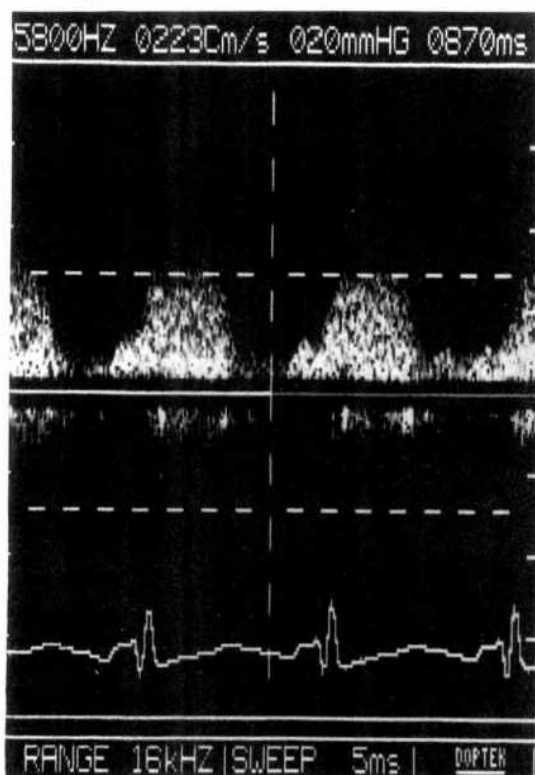


Fig 2 Spectral signal of flow through a ventricular septal defect in a patient with high pulmonary artery pressure and thus a small pressure difference between the ventricles. The marker line indicates the maximum velocity of 2.23 m/s, equivalent to a pressure difference of 20 mm Hg.

of the high pass filter (maximum 5000 Hz with the Doppler spectrum analyser) to exclude high amplitude, low frequency signals that can obscure the high frequency, lower amplitude signals that occur with a small ventricular septal defect.

Doppler gradients ranged from 0 to 110 mm Hg. A Doppler signal of flow through the ventricular septal defect was not recorded in one infant with a peak to peak gradient of 30 mm Hg. This infant with multiple defects was examined early in the study with a non-imaging transducer; in retrospect it seems likely that more experience and an assiduous examination technique would have permitted the signal to be recorded.

COMPARISON OF DOPPLER AND MEASURED GRADIENTS

The practical value of the technique was assessed by calculating the difference between the Doppler and measured gradients and comparing these values with the average value of the two measurements.⁸ The mean difference (2 SD) between the measurements was as follows: Doppler minus peak to peak for total population ($n = 103$), -0.9 (26.2) (fig 4); Doppler minus peak to peak measured with two catheters ($n = 41$), -3.1 (24.4); Doppler minus instantaneous maximum ($n = 41$), -8.3 (24.6) (fig 5).

Thus comparison of Doppler against peak to peak gradient in the total population shows that if the infant in whom no signal was obtained is excluded, the gradient was underestimated by > 15 mm Hg in only those with a mean pressure drop of greater than 50 mm Hg; this underestimate was > 20 mm Hg in eight and between 15 and 20 mm Hg in five (fig 4).

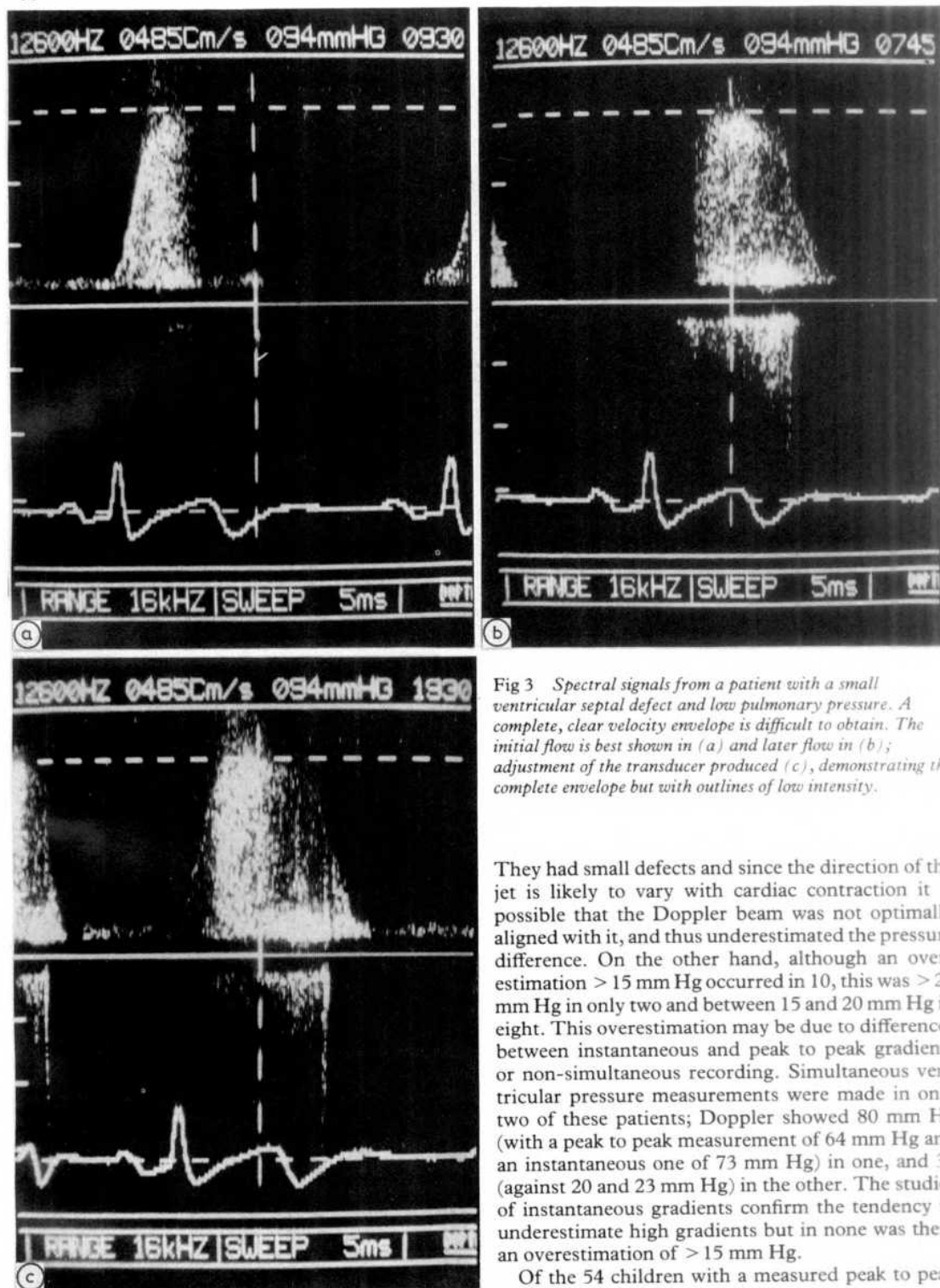


Fig 3 Spectral signals from a patient with a small ventricular septal defect and low pulmonary pressure. A complete, clear velocity envelope is difficult to obtain. The initial flow is best shown in (a) and later flow in (b); adjustment of the transducer produced (c), demonstrating the complete envelope but with outlines of low intensity.

They had small defects and since the direction of the jet is likely to vary with cardiac contraction it is possible that the Doppler beam was not optimally aligned with it, and thus underestimated the pressure difference. On the other hand, although an overestimation > 15 mm Hg occurred in 10, this was > 20 mm Hg in only two and between 15 and 20 mm Hg in eight. This overestimation may be due to differences between instantaneous and peak to peak gradients or non-simultaneous recording. Simultaneous ventricular pressure measurements were made in only two of these patients; Doppler showed 80 mm Hg (with a peak to peak measurement of 64 mm Hg and an instantaneous one of 73 mm Hg) in one, and 36 (against 20 and 23 mm Hg) in the other. The studies of instantaneous gradients confirm the tendency to underestimate high gradients but in none was there an overestimation of > 15 mm Hg.

Of the 54 children with a measured peak to peak

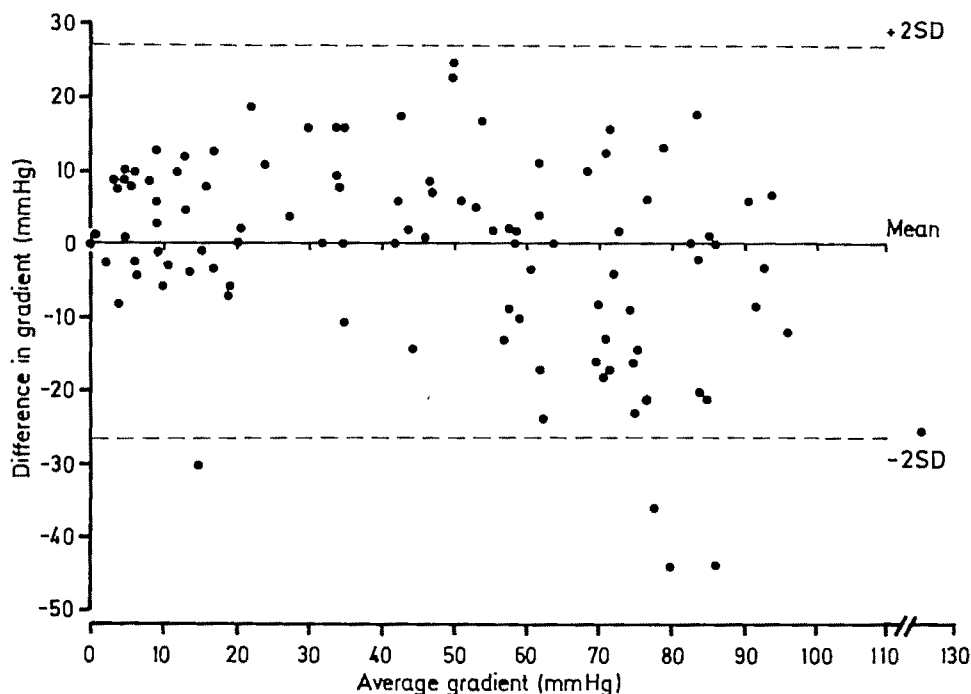


Fig 4 Comparison of the difference between pressure drops (Doppler minus peak to peak) against the average gradient in all 103 patients.

gradient of < 50 mm Hg, all but four were aged < 2 . The pressure drop was underestimated by > 15 mm Hg in only the infant with multiple muscular ventricular septal defects in whom no definite flow signal was reported; since the right ventricular pressure would have been overestimated pulmonary hypertension would not have been missed. This child was seen early in the study and it is uncertain whether the failure to pick up the signal was because multiple defects were present or because of lack of experience in the technique. There was overestimation of the peak to peak pressure drop by > 15 mm Hg, with the possibility of underestimating pulmonary artery pressure, in seven of these 54, including one of the four with an average difference of < 25 mm Hg. None the less, in all 11 with an average difference of < 50 mm Hg in whom simultaneous studies against instantaneous gradient were made these were within 13 mm Hg of each other.

Discussion

In patients with a ventricular septal defect echocardiography provides an anatomical diagnosis but is unable to give accurate information on haemodyn-

amic function. Doppler ultrasound can confirm the site of a ventricular septal defect and, more importantly, measure blood flow velocity. Volumetric flow and pressure difference can be derived from this information. It may help to determine the need for surgical closure in the infant or young child or for prophylaxis against infective endocarditis in the older patient.

The assessment of pulmonary artery pressure with Doppler ultrasound has been reported but as yet no method has been accepted as reliable. Our experience suggests that in patients with a ventricular septal defect a straightforward and repeatable method that may be suitable for routine use is the measurement of the pressure drop from the left to right ventricle. It is presumed that the systemic blood pressure approximates to the left ventricular systolic pressure and that subtraction of the interventricular gradient from this should give the right ventricular, and in the absence of pulmonary stenosis, the pulmonary arterial systolic pressure. The distal systolic blood pressure, however, can be higher than that in the left ventricle and ascending aorta,⁹ and in addition in young children accurate measurement of blood pressure with an arm cuff can be difficult.

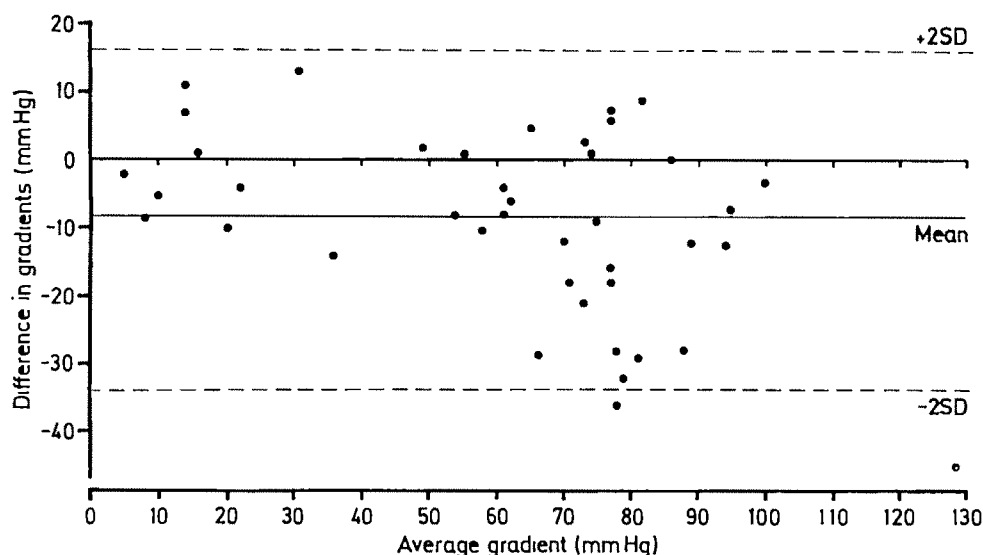


Fig 5 Comparison of the difference between pressure drops (Doppler minus instantaneous) against the average gradient in the 41 patients in whom pressures were measured simultaneously with two catheters.

This study has not attempted to compare arm and left ventricular pressures or accurately to calculate right ventricular pressure but has sought simply to assess the accuracy of Doppler measurement of the drop in pressure from the left to the right ventricle. There are several reasons why Doppler assessment of this might be inaccurate. If the beam is not aligned along the line of flow, the maximum blood velocity and thus the pressure drop will be underestimated with subsequent overestimation of the right ventricular and pulmonary arterial pressures, but pulmonary hypertension would not be missed. Doppler measures the instantaneous maximum and not the peak to peak gradient and, particularly in aortic stenosis, this can result in Doppler giving a significantly higher value than direct measurement of the peak to peak value.¹⁰ If there were similar differences in patients with a ventricular septal defect Doppler overestimation of the pressure drop could occur and the consequent underestimation of the pulmonary artery peak systolic pressure would have potentially dangerous results. This study has shown a relatively good correlation between the Doppler and measured gradients. As was found by Hatle and Rokseth² there was a tendency to underestimate high gradients; this was not confirmed in the other studies.^{6,7} Although the instantaneous pressure drops were higher than the peak to peak ones, this difference was small and not of clinical importance in the more important group with high pulmonary artery pressure.

The most valid comparison of pressure drops is obtained from Doppler studies performed simultaneously with pressure measurement from two catheters. The dual catheter results (fig 5) confirm the tendency of Doppler to underestimate the pressure drop in those with small defects and low right ventricular pressures. There is little evidence of overestimation of the drop in this group and indeed, for the instantaneous pressure drop the maximum overestimation by Doppler was only 13 mm Hg (Doppler gradient 36 mm Hg and catheter 23 mm Hg instantaneous and 20 mm Hg peak to peak). Although only eight patients with an average gradient <25 mm Hg had dual catheter studies it seems likely that in general in this group the instantaneous pressure difference is little different from the peak to peak one.

Measurement of blood pressure in infants can present problems; the presumption that the systolic blood pressure in the arm equates with the left ventricular pressure adds a further error, calling into question the reliability of the measurement of right ventricular pressure.

It seems appropriate, however, to draw some conclusions from this study. If it is accepted that most patients who are less than two years old will have a systolic blood pressure of 65 to 110 mm Hg (5th–95th centile)¹¹ and that those with a right ventricular pressure <50% of the left will not require operation the following suggestions can be made. A Doppler recording of <30 mm Hg is likely

to be associated with a right ventricular, and thus pulmonary artery pressure, of $>50\%$ of systemic level, suggesting that operation is likely to be necessary, while a recording of >55 mm Hg suggests right ventricular pressure of $<50\%$ of the systemic level and that operation can be deferred. But in patients with a Doppler record of between 30 and 55 mm Hg Doppler as yet has not been shown to be sufficiently accurate to identify those who require operation and those who do not; in these patients it is appropriate to attempt to measure blood pressure and Doppler simultaneously, with the child sedated if necessary. While more information is awaited it is appropriate in this area of uncertainty to undertake further investigations, including cardiac catheterisation. In view of the small number of patients with pulmonary hypertension studied with two catheters further studies are necessary to confirm that there is not a clinically significant difference between peak to peak and instantaneous pressure drops in those with pulmonary hypertension and that this observation is unaffected by pulmonary vascular resistance and shunt size. Thus clinical decisions must take into account all the accepted clinical and non-invasive techniques in routine use.

In the symptom free older child with a systolic murmur at the lower left sternal edge clinical examination often provides reliable evidence of a ventricular septal defect; in some it can be difficult to differentiate between an innocent murmur and a small ventricular septal defect. In all our patients with a ventricular septal defect and normal right ventricular pressure Doppler demonstrated the jet, even where the defect was not evident on echocardiography and in one where the very small defect was barely shown on left ventricular angiography. This is in keeping with previous findings² and confirms that Doppler is an extremely sensitive technique for detecting the presence of flow through a small ventricular septal defect. This should allow a more effective approach to the management of the symptom free patient; the exclusion of a ventricular septal defect should prevent unnecessary follow up and antibiotic prophylaxis against infective endocarditis.

Although the extremes of high or normal right ventricular pressure are easily determined with clinical and other non-invasive studies in patients with a ventricular septal defect, we consider that Doppler measurement of the ventricular pressure difference is

of practical value and significantly adds to the precision of the full non-invasive assessment. We are now convinced that it has become essential in the initial investigation of patients with a ventricular septal defect and is of particular value in the assessment and subsequent follow up of the infant and young child.

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A new technique for the assessment of pulmonary regurgitation and its application to the assessment of right ventricular function before and after repair of tetralogy of Fallot

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SUMMARY Biplane right ventriculograms with simultaneous high fidelity pressure recordings were obtained in 24 patients with tetralogy of Fallot. Twelve patients were studied before repair and 12 were studied 67 (42) months after radical surgical repair without the use of a transannular patch. In the patients who had repair right ventricular end diastolic and end systolic volume indices were higher, and the ejection fraction was lower. Time to peak ventricular filling and the peak rate of ventricular filling were also lower in this group and there was a significant relation between peak filling rate and ejection fraction. Postoperative pressure-volume loops from nine patients showed an increase in cavity volume during the decline in right ventricular pressure, which indicated pulmonary regurgitation. The mean regurgitant volume for the group correlated with end diastolic volume index, stroke volume index, and peak filling rate, but not with ejection fraction.

These data show that both systolic and diastolic abnormalities of right ventricular function are detected in most patients after radical repair of tetralogy of Fallot. The reduction of ejection fraction previously reported in these patients is unrelated to the degree of pulmonary regurgitation and primarily reflects an impairment of contractile function that presumably is related to intraoperative events.

Tetralogy of Fallot accounts for approximately 10% of all cases of congenital heart disease. The introduction of systemic to pulmonary shunt procedures in the late 1940s revolutionised the treatment of these patients. Nowadays most patients have surgical correction, often without prior systemic to pulmonary shunting.¹ Surgical mortality is low and short term relief of symptoms excellent.² The operation is performed under cardiopulmonary bypass, usually via a right ventriculotomy, and in recent years interest has centred around the effects of operation on ventricular function. Before repair left ventricular function was abnormal in many patients,^{3,4} but it did not deteriorate after operation.³ The reverse seems to be true for right ventricular function. Right ven-

tricular volumes and ejection fractions were normal before operation,^{3,5} but deteriorated after repair.^{3,6-9} To date the cause of this deterioration in right ventricular function after corrective operation has not been adequately explained. Residual right ventricular volume load (pulmonary regurgitation or residual ventricular septal defect), chronic hypoxia before operation, and the direct effects of right ventriculotomy have all been implicated.^{3,7-9} Previous studies were restricted to measurements of ejection fraction with or without measurements of end diastolic and end systolic volumes, and patient subgroups were often poorly defined, making interpretation of their results difficult. Furthermore, there are no data on other indices of right ventricular function such as ventricular filling and emptying rates and pressure-volume relations, which may provide additional information on the pathogenesis of any abnormalities of function.

We studied right ventricular function in two discrete groups of patients. Twelve were studied

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before repair and 12 symptom free patients, in whom there was no evidence of residual ventricular septal defect or significant right ventricular outflow tract obstruction, were studied after repair. Because we obtained simultaneous pressure and volume data we were able to compare indices of systolic and diastolic function other than ejection fraction and simple ventricular volumes. We were also able to assess the volume of pulmonary regurgitation and its effects.

Patients and methods

GROUP 1

We studied 12 patients aged from eight months to seven years (mean (SD) 42.2 (28) months) before definitive repair. In six patients a modified Blalock shunt had been performed 14 (11) months before because of severe hypercyanotic attacks in infancy. The remainder were studied before any operation. No patient was taking cardioactive medication. Arterial oxygen saturation at the time of cardiac catheterisation ranged from 69% to 95% and the haemoglobin concentration was 158 (20) g/l. Right ventricular peak systolic pressure was 68 (7) mm Hg and right ventricular end diastolic pressure was 5 (3) mm Hg. All patients were undergoing cardiac catheterisation under general anaesthesia as a routine part of their assessment before radical surgical repair.

GROUP 2

We studied the 12 patients in this group (age 89 (54) months) 67 (42) months after definitive repair. They were all symptom free, leading unrestricted lives, and taking no medication. They were selected on an informal basis when they presented for routine out patient follow up; parents gave their informed consent for follow up cardiac catheterisation in each child. All operations were performed with surface cooling and during cardiopulmonary bypass. We repaired the ventricular septal defect and enlarged the right ventricular outflow tract via a right ventriculotomy. In one patient relief of outflow tract obstruction was satisfactory without an outflow tract patch, but in the remainder the outflow tract was widened with a synthetic graft (woven Dacron). None of the patients had transannular repair (extending the patch across the pulmonary valve annulus). Six patients already had systemic-to-pulmonary shunts because of severe hypercyanotic attacks in infancy. These were taken down at the time of repair.

On clinical examination early diastolic murmurs were audible in four of the patients and short systolic murmurs were present over the pulmonary area in six. The postoperative electrocardiogram showed complete right bundle branch block in all patients.

No patient had electrocardiographic or clinical evidence of arrhythmia. The haemoglobin concentration was lower than in group 1 (124 (9) g/l, $p < 0.001$). Cardiac catheterisation was performed during general anaesthesia with alphaxalone-alphadolone acetate (Althesin) after premedication with trimeprazine. Mean (SD) aortic oxygen saturation was 97 (1)% and there was no evidence of intracardiac shunting in any patient. The right ventricular systolic pressure in this group was 32 (7) mm Hg, and only two patients had peak systolic pressures of > 40 mm Hg (44 and 48 mm Hg respectively). Right ventricular end diastolic pressure was not significantly different from that in group 1 (6 (3) mm Hg). The peak to peak right ventricle to pulmonary artery pressure drop was < 20 mm Hg in all patients (mean 7 mm Hg, range 0–19).

METHODS

Angiography

Biplane right ventriculograms were obtained in the 30° right anterior oblique and 60° left anterior oblique projections after the injection of 1.0–1.5 ml/kg of radiographic contrast medium. The cineangiograms were recorded at a frame rate of 50 frames per second when the heart rate was less than 100 beats per minute, and 75 frames per second when the heart rate exceeded 100 beats per minute. A mark, coinciding with the R wave of the patient's electrocardiogram was recorded on the film. At the end of the study we performed a calibration sequence. This consisted of recording the effect of a 10 cm shift of the patient perpendicular to the two image intensifiers. This was done immediately after angiography, while the catheter remained in the right ventricle. Thus the magnification factor for each view could be calculated from the shift of the catheter tip according to the formula:

$$\text{Magnification factor} = \frac{\text{observed shift (cm)}}{10 \text{ cm}}$$

This method has advantages over those that use grids or calibration objects because no assumptions need to be made about the position of the ventricle.

Pressure measurements

Pressure was measured simultaneously with the biplane ventriculograms by use of 5F or 7F micromanometer tipped catheters (Millar Instruments Inc). The 7F catheter incorporated a fluid filled lumen. The 5F catheters did not have a fluid filled lumen and when these catheters were used ventriculography was performed with a fluid filled catheter, usually introduced into the right ventricle retrogradely from the femoral artery, or anterogradely via the ipsilateral femoral vein. The

micromanometers were calibrated against an electrical reference before insertion and checked against the pressure recorded via the fluid filled catheter after insertion. Recordings were made on paper at 100 or 200 mm/s along with the patient's electrocardiogram and a mark coinciding with the appearance of contrast medium in the ventricle. Recordings were available from all patients in group 1 and in 11 of the 12 patients studied in group 2.

Analysis

We excluded all extrasystoles, all complexes that immediately followed extrasystoles, and all complexes recorded during injection of contrast. Angiograms were manually digitised frame by frame throughout the selected cycle in both angiographic views by a Summagraphics digitising plate interfaced with a Prime 750 computer. Right ventricular volumes were calculated from the biplane ventriculograms and corrected by regression equations obtained from a cast study previously described in detail.¹⁰ Briefly, our method for measuring right ventricular volume divides the ventricle into 40 equal slices along its long axis. Each slice is assumed to be an ellipsoid (with the major and minor dimensions derived from the two angiographic projections). Figures 1 and 2 show examples of computer derived three dimensional constructions obtained by this method. The consistent overestimation of actual volume can be corrected by applying the appropriate regression equation (for 30° right anterior oblique and 60° left anterior oblique projections; actual volume = 0.82 (calculated volume) + 0.68 ml, $r = 0.99$, $p < 0.001$, SEE (4) ml).¹⁰ The corresponding pressure trace was digitised by the same equipment and stored on magnetic tape, along with the volume data, for later analysis.

We derived the following variables from these stored data:

(a) Right ventricular end diastolic volume index—

This was taken as the maximum value on the volume-time curve (see fig 3) and corrected for body surface area (expressed in ml/m²). End systolic volume was taken as the minimum cavity volume and was similarly standardised for body surface area. Stroke volume index (SVI) was calculated as: $SVI = \text{end diastolic volume index} - \text{end systolic volume index}$ (ml/m²).

(b) Right ventricular ejection fraction—This was calculated in the usual way: $\text{ejection fraction} = \text{stroke volume} \div \text{end diastolic volume} \times 100 (\%)$.

(c) Right ventricular filling and emptying rates—These values were obtained from the first derivative of the volume-time curve. The raw volume data were first smoothed by a three point moving-average filter and then differentiated with respect to time (fig 4).

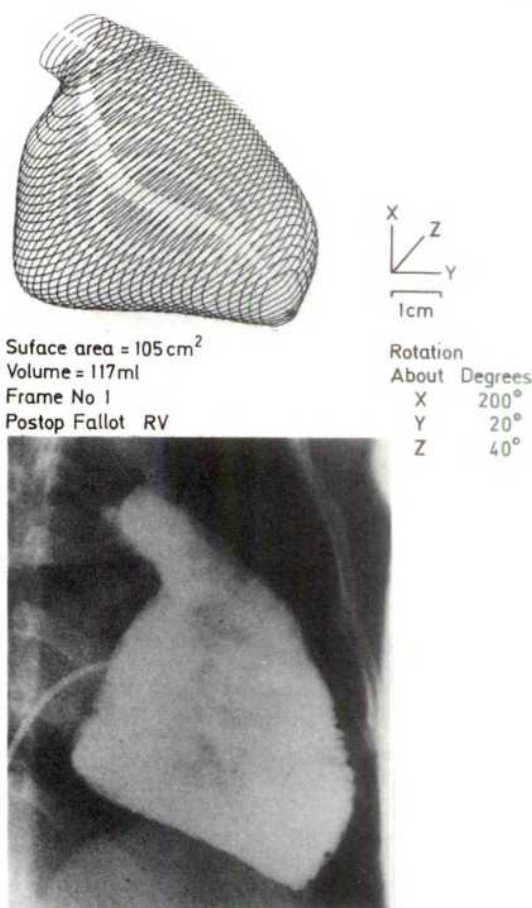
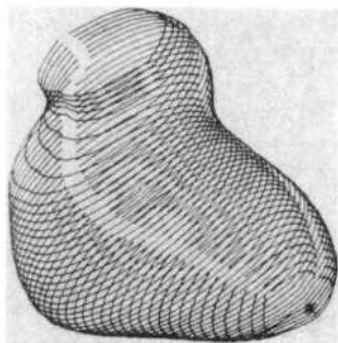


Fig 1 Computer derived three dimensional reconstruction of the right ventricle obtained from a patient after repair. The right oblique view of the biplane angiogram is shown for comparison.

The curve generated has a negative component corresponding to ventricular emptying, a biphasic positive deflection corresponding to an early passive phase of ventricular filling, and a later deflection corresponding to filling resulting from atrial contraction. The peak ventricular filling rate during passive filling was taken as the peak positive deflection during the initial early filling phase. Occasionally only one peak was seen, especially at higher heart rates, and under these circumstances the maximum value of the single peak was used. Peak rates of filling and ejection were standardised by dividing by end diastolic and stroke volumes (units s⁻¹).

(d) The time taken to reach peak ejection and peak filling rates was also recorded. Time to peak ejection was measured as the time from the Q wave of the



Surface area = 80 cm^2
 Volume = 85 ml
 Frame No 1
 Postop Fallot

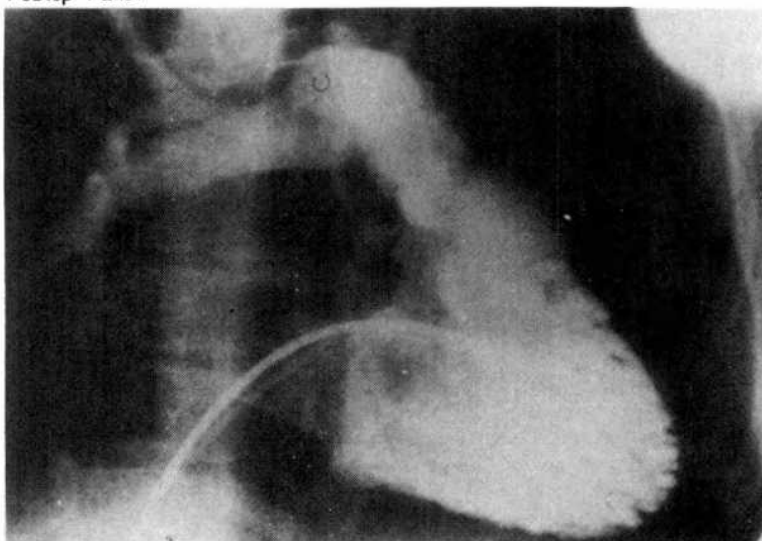


Fig 2 Three dimensional reconstruction from a patient with a discrete aneurysm of the right ventricular outflow tract.

electrocardiogram to the time of peak ejection. Time to peak filling was measured as the time from the point where the $DVol/Dt$ curve crossed the zero line to the time of peak filling rate.

(e) *Pressure volume loops*—These were constructed by combining the simultaneous pressure and volume curves. The construction and interpretation of these loops is described in detail in a previous publication.¹⁰

Systolic stroke work was measured from the loops by automatic planimetry of the area enclosed by the loop and subsequently corrected for body surface area ($J/\text{beat}/\text{m}^2$). The cycle efficiency is the ratio of the area of the loop to that of a square or rectangle that would just enclose it¹¹—that is, the ratio of actual

stroke work to the maximum work possible for a ventricle with the same pressure characteristics and stroke volume.

Assessment of pulmonary regurgitation

Measurement of pulmonary regurgitation from pressure-volume loops has not been described before. In nine of the 11 loops obtained from patients studied after definitive repair we saw an increase in right ventricular volume during a fall in pressure (fig 5). Ventricular filling began when right ventricular pressure was well above that of peak right atrial pressure. In the absence of filling through the tricuspid valve, through a ventricular septal defect (excluded by oximetry and angiography), or by

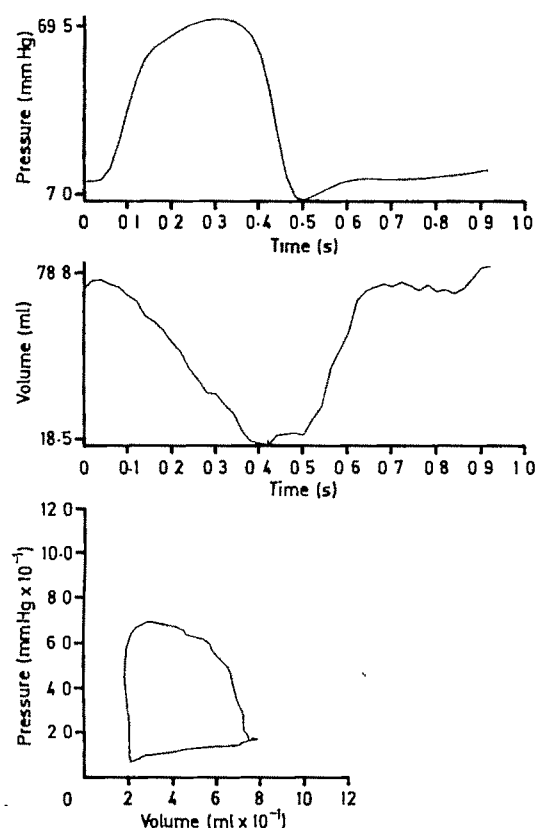


Fig 3 Plots showing simultaneous pressure and volume curves throughout the cardiac cycle. The resultant pressure-volume loop, taken from a preoperative patient, shows a well defined period of isovolumic relaxation with no evidence of volume increase during pressure decline (fig 5).

continued injection of radiographic contrast (we analysed only beats occurring after the end of injection), this increase in ventricular volume must be secondary to pulmonary regurgitation. The pulmonary regurgitant volume during the pressure fall was measured as the change in volume that occurred between the point of minimum cavity dimension to the point where right ventricular pressure had fallen to a level equivalent to that of peak right atrial pressure (recorded before angiography). This volume was expressed in absolute terms (ml/beat/m² body surface area) or as a percentage of the total stroke volume. A pulmonary regurgitant volume of >5 ml/beat/m² body surface area was considered to be significant.

STATISTICAL ANALYSIS

Variables were expressed as the mean (1 SD). We

used standard *t* tests to compare normally distributed group data, and the Mann-Whitney U test when normal distribution of the data could not be demonstrated. The null hypothesis was rejected when $p < 0.05$. We tested for correlation between variables by linear regression analysis by the method of least squares.

Results

Tables 1 and 2 show the raw data for each patient. Right ventricular end diastolic volume index was significantly higher in group 2 than in group 1 (63.3 (17.7) v 88.1 (33) ml/m², $p < 0.05$). End systolic volume index was also higher after definitive repair (23.7 (11.1) v 41.3 (18.6) ml/m², $p = 0.012$); and although there was a tendency towards a high stroke volume in group 2 this difference was not statistically significant (39.6 (13.1) v 46.7 (16.3) ml/m², $p = \text{NS}$).

When the subgroup of unoperated patients in group 1 was compared with those with shunts there was a tendency for end diastolic volume index to be increased in the group with shunts (60 (21) v 66 (14) ml/m²) and for ejection fraction to be lower (65 (8) v 59.5 (13)) but neither of the differences was statistically significant. Right ventricular ejection fraction was lower after repair (62.4 (11.1) v 53.8 (6.5), $p < 0.05$) and correlated significantly with end systolic volume ($r = -0.72$, $p < 0.01$) and peak filling rate ($r = 0.56$, $p < 0.05$) in this group.

Peak rate of ejection corrected for end diastolic volume was significantly lower in patients studied after repair (4.2 (1.4) v 2.6 (0.5) s⁻¹, $p < 0.005$). Peak rate of ventricular filling corrected for end diastolic volume or stroke volume was also reduced after repair (6.4 (2.6) v 3.6 (1.4), $p < 0.01$ and 10.3 (3.9) v 6.66 (2.0), $p < 0.001$, respectively). Time to peak filling rate was shorter in group 2 patients (104 (39) v 69 (29) ms, $p = 0.02$) but time to peak ejection rate was similar in the two groups ($p = \text{NS}$). There was no significant difference in RR interval between the

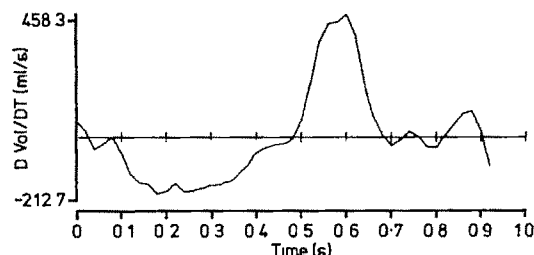


Fig 4 First derivative of the volume curve shown in fig 3. Peak rates of ventricular filling ($D\text{Vol}/DT$) and emptying ($-D\text{Vol}/DT$) are shown on the y axis.

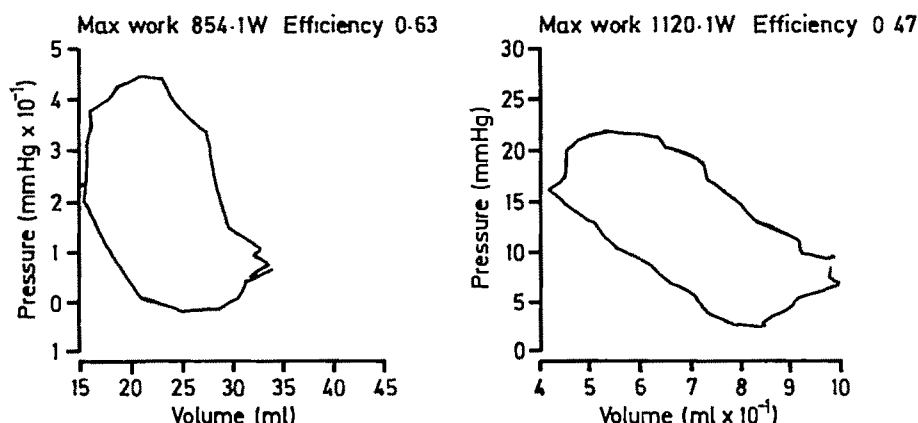


Fig 5 Pressure-volume loops obtained from two patients after repair. In both patients right ventricular volume increased as pressure fell. This represents pulmonary regurgitation and is more severe in the loop shown on the right.

two groups (group 1 567 (169) v 657 (149) ms, $p = \text{NS}$).

There was no relation between any of these variables and the age at operation in group 2 but there were weak, non-significant relations between the age at study and end diastolic volume index, and a significant inverse relation with ejection fraction ($r = 0.49$ and -0.5 respectively, both $p < 0.1$).

PRESSURE-VOLUME RELATIONS

We have already described the changes in shape and characteristics of the right ventricular pressure-volume loop with pressure load.¹² In this study a typical loop obtained before repair was more square or rectangular than the triangular or trapezoidal normal right ventricular pressure-volume loop which shows a well defined period of truly

"isovolumic" relaxation. After repair and relief of pressure load, the shape of the loops became more normal (fig 5). The reduction in cycle efficiency (71 (7) v 56 (9), $p < 0.001$) and systolic stroke work (1.9 (0.75) v 0.6 (0.34) J/beat/m² body surface area, $p < 0.001$) reflected these changes.

In nine of the 11 group 2 (repair) patients pulmonary regurgitation was seen as an increase in ventricular volume during pressure fall (see methods section). The pulmonary regurgitant fraction for the group was 28 (19%) of the stroke volume. Pulmonary regurgitant volume was 15.5 (14) ml/beat/m² and correlated with end diastolic volume index ($r = 0.78$, $p < 0.01$) and stroke volume index ($r = 0.85$, $p < 0.001$) but not with ejection fraction ($r = 0.01$, $p = \text{NS}$) (fig 6). There was a weaker, but significant, inverse relation between peak filling rate and pulmonary regurgitant volume ($r = -0.54$, $p < 0.05$).

Table 1 Data of 12 patients with tetralogy of Fallot (group 1)

Case No	Shunt	Age (month)	EDVI (ml/m ²)	ESVI (ml/m ²)	SVI (ml/m ²)	EF (%)	PER/EDV (s ⁻¹)	tPER (ms)	PFR/EDV (s ⁻¹)	tPFR (ms)	RR (ms)
1	-	8	72	33	39	53	4.7	130	7.4	120	700
2	+	12	85	39	46	54	3.2	130	10.5	60	480
3	-	19	36	12	24	66	5.0	123	5.2	100	600
4	+	24	52	11.5	40.5	77	4.6	123	7.25	100	560
5	-	47	92	19	73	73	7.6	100	11.1	50	360
6	+	72	52	12	40	76	4.3	150	8.2	40	460
7	-	84	67	17	50	74	2.7	180	5.8	180	920
8	+	36	59	26	33	54	3.2	100	2.9	110	600
9	+	48	81	41	40	48	2.6	100	3.7	120	500
10	+	13	70	36	34	48	2.8	210	3.5	120	800
11	-	84	56	24	32	58	4.4	150	6.2	110	400
12	-	60	38	14	24	63	5.0	140	5.2	140	420
Mean (SD)		42 (28)	63 (18)	24 (11)	40 (13)	62 (11)	4.2 (1.4)	136 (33)	6.4 (2.6)	104 (39)	567 (169)

EDVI, end diastolic volume index; EF, ejection fraction; ESVI, end systolic volume index; PER, peak ejection rate; PFR, peak filling rate; SVI, stroke volume index; tPER, time to PER; tPFR, time to PFR.

Table 2 Data on 12 patients after repair of tetralogy of Fallot (group 2)

Case No	Shunt	Age (mnth)	EDVI (ml/m ²)	ESVI (ml/m ²)	SVI (ml/m ²)	EF (%)	PER/EDV (s ⁻¹)	tPER (ms)	PFR/EDV (s ⁻¹)	tPFR (ms)	RR (ms)
1	+	108	71	38	33	46	3.3	110	3.4	50	500
2	-	36	42	15	27	64	3.4	200	6.3	40	700
3	+	120	50	18.5	31.5	63	2.7	80	4.4	50	700
4	-	180	136	17.9	57	42	2.0	110	2.2	30	780
5	+	24	53	23.5	29.5	55	3.0	120	5.1	100	480
6	+	19	91	45	46	50	3.6	110	4.8	60	440
7	-	120	101	47	54	53	2.0	70	2.0	60	640
8	-	132	91	46	45	49	2.2	150	2.6	110	920
9	-	36	127	52	75	59	2.7	100	2.6	50	780
10	+	108	106	47	59	55	2.2	150	3.5	90	800
11	+	48	59	25	34	57	2.7	170	4.5	120	540
12	-	144	130	60	70	53	2.0	100	2.3	70	600
Mean (SD)		90 (54)	88 (33)	41 (19)	47 (16)	54 (6.5)	2.6 (0.5)	114 (37)	3.7 (1.4)	69 (29)	657 (149)

See footnote to table 1 for abbreviations

Discussion

We calculated right ventricular volume by applying the regression equations obtained in a previous study that compared the right ventricular volume of a cast measured by fluid displacement with the volume derived from biplane angiograms.¹⁰ This regression equation may give rise to errors if loading conditions or the myocardium are abnormal. Such errors are likely to be small, however,¹³ and fig 2 shows the advantages of our multiple slice method under such circumstances. It is possible that other multiple slice methods such as those where the right ventricle is divided into only 10 slices^{13,14} or those with a fixed slice depth of 0.5 cm¹⁵ may not take account of small variations in ventricular shape (as in this case where

there is an outflow tract aneurysm). We divided the right ventricle into 40 slices, which ensured that such abnormalities were incorporated into the volume calculation. Furthermore, small errors in the estimation of absolute volume should not have influenced measurements of relative changes in volume. We believe that this is a justifiable method of measuring frame by frame changes in right ventricular volume.

Two previous preoperative studies in patients with tetralogy have shown that right ventricular end diastolic volume and ejection fraction are essentially normal.^{3,5} A systemic to pulmonary shunt, however, results in a higher right ventricular volume and lower ejection fraction.⁵ The results of the present study largely confirm these findings; end diastolic volume corrected for body surface area and ejection fraction

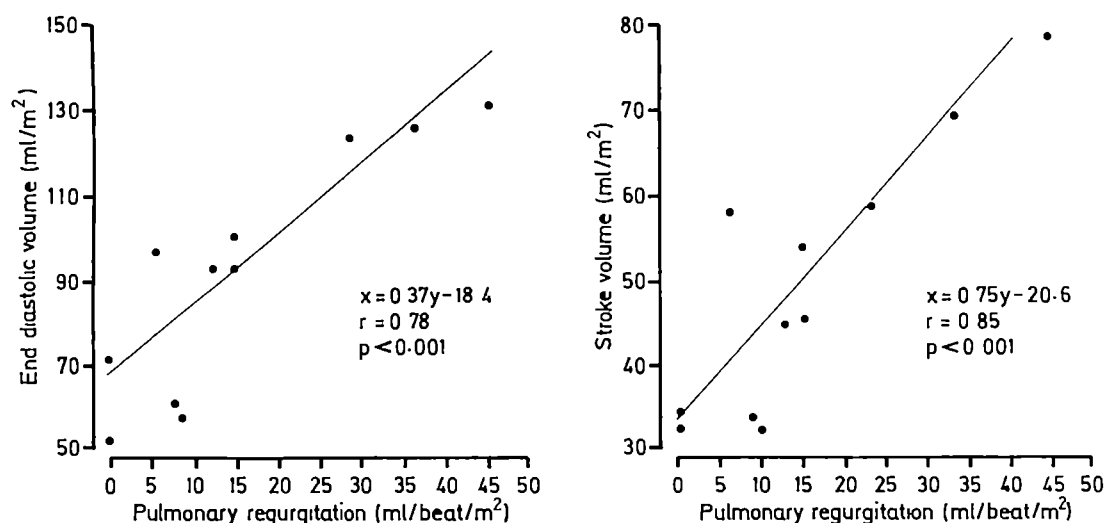


Fig 6 Graphs showing the relation between pulmonary regurgitant volume and end diastolic volume index (left) and end systolic volume index (right).

were not significantly different from normal values,¹⁴ but there was a tendency for end diastolic volume to be higher and for ejection fraction to be lower in the six patients with a modified Blalock-Taussig shunt than in the patients without a shunt.

Right ventricular end diastolic volume was increased and the ejection fraction was lower in the group that had a repair operation. Similar changes have been demonstrated by others.^{3,7,8} It has been suggested that these may be the result of a primary myocardial abnormality,³ secondary to the diffuse myocardial fibrosis that was found in these patients.¹⁶ Some workers,⁸ but not others,⁶ have shown a lower ejection fraction in the subgroup of patients who require right ventricular outflow tract patching than in those who require only an infundibulectomy. The effect of residual right ventricular volume load is also important.^{3,7,9} The most frequent cause of this will be pulmonary regurgitation, because disruption of the architecture of the outflow tract and pulmonary valve at the time of repair is almost inevitable. This is supported by the data in the present study which show that up to 85% of patients have significant pulmonary regurgitation, often in the absence of clinical signs. Unfortunately previous studies of the effect of pulmonary regurgitation are difficult to interpret. This is largely because of the difficulty investigators experienced in quantifying the degree of regurgitation present. In one study, where pulmonary regurgitation was assessed clinically, there was a significant reduction in right ventricular ejection fraction when it was "moderate or severe".⁹ In another, where it was assessed subjectively from pulmonary root angiograms, the degree of pulmonary regurgitation was not related to ejection fraction.⁷ The methods used in both these studies are subject to criticism. Lange *et al* used a videodensitometric method to assess the degree of pulmonary regurgitation in their patients after repair.³ Their study showed that as the volume load increased the ejection fraction fell (however, there is a discrepancy between the results in their tables and those shown in the text and figures). It was difficult to interpret the results of this study because they grouped together data from patients with right ventricular volume load caused by pulmonary regurgitation, residual ventricular septal defect, or both (a method of analysis which was subsequently criticised¹⁷) and they included patients with large residual outflow tract gradients (the mean outflow tract gradient was > 17 mm Hg in all their postoperative subgroups).

The results of our study go some way to answering several questions about the pathophysiology of right ventricular dysfunction after repair of tetralogy of Fallot.

We selected our patients chiefly because they were symptom free, and we studied only patients who

Redington, Oldershaw, Shinebourne, Rigby

showed no residual ventricular septal defect or important obstruction of the right ventricular outflow tract. In 11 of the 12 patients the outflow tract was enlarged with a patch but none required transannular patching. They were, therefore, a relatively uniform population.

We were also able to get an accurate estimate of the volume of pulmonary regurgitation from the pressure-volume loops. Nine of the 11 patients in whom we obtained pressure-volume loops had an increase in right ventricular volume of > 5 ml/beat/m² during the decline in right ventricular pressure. The increase in volume before the point at which the right ventricular pressure was equivalent to the peak right atrial pressure—that is before the tricuspid valve could open—must represent pulmonary regurgitation (in the absence of left to right shunting or continued injection of contrast medium). And although this volume is not the total regurgitant volume, it should be an accurate index of the degree of regurgitation.

We found a highly significant correlation between pulmonary regurgitant volume and both end diastolic volume and stroke volume index, but no relation with ejection fraction. Although this observation is at variance with the findings of Lange *et al*³ the methodological weaknesses of their study make it difficult to compare data. Furthermore, some of Lange *et al*'s patients had much greater right ventricular volume load than our patients. Indeed there was no significant difference between their two subgroups with less severe volume loading, which suggests that there may be a threshold above which pulmonary regurgitation reduces ejection fraction.

What then is the cause of the reduced ejection fraction in most patients after repair of tetralogy of Fallot? It would be surprising if the contractile properties of the right ventricle were not altered when part of its wall is replaced with a non-contractile material. We may not need to invoke a possible adverse effect of pulmonary regurgitation. Graham *et al* show that there was no difference in ejection fraction after repair if an outflow tract patch was not used.⁸ Those who do not require outflow tract patching may be less likely to have postoperative pulmonary regurgitation, but unfortunately Graham *et al* were unable to quantify the degree of pulmonary regurgitation in their patients. Their findings and our own data, showing no correlation between pulmonary regurgitation and right ventricular ejection fraction and no difference in ejection fraction between the group of six patients with the lower regurgitant volumes and the remainder seem to suggest that the direct effects of operation are most important.

We suggest that the impairment of ventricular function in most patients after repair of tetralogy of

Fallot is primarily an effect of the non-contractile outflow tract patch rather than a consequence of mild or moderate pulmonary regurgitation. This suggestion is also supported by our finding that despite relief of right ventricular outflow tract obstruction, the peak rate of right ventricular ejection was also reduced after repair but was unrelated to the degree of pulmonary regurgitation.

In addition to these systolic abnormalities there were also abnormalities of diastolic function. Peak rate of ventricular filling and the time to peak filling were both significantly reduced in the repair group (group 2). This pattern is similar to that previously described for the left ventricle with ischaemic cardiomyopathy.¹⁸ Although this pattern may be explained by a reduction in diastolic compliance of the right ventricular myocardium secondary to the patch or myocardial fibrosis, it is perhaps more likely to be related to the higher end systolic volume of the right ventricle and its further distension before tricuspid valve opening, resulting from pulmonary regurgitation. The normal right ventricular end diastolic pressures and the strong inverse relation between peak filling rate and end systolic volume index in the repair group (but not in group 1) support this suggestion; however, it is likely that a combination of factors contributes to the overall impairment.

We found abnormalities of both systolic and diastolic indices of right ventricular function after repair of tetralogy of Fallot and a strong linear relation between the amount of pulmonary regurgitation and right ventricular end diastolic volume. The reduction in right ventricular ejection fraction after repair seemed to be related to the direct effects of operation rather than to pulmonary regurgitation in this selected group of patients. The effect of more severe or more prolonged postoperative pulmonary regurgitation is unknown. Further long term studies would be helpful.

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Neonatal anatomical correction of transposition of the great arteries: non-invasive assessment of haemodynamic function up to four years after operation

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SUMMARY Intracardiac and great artery blood flow velocities were recorded by pulsed and continuous wave Doppler ultrasound in 18 children aged between eight months and four years (mean 25 months) who had undergone anatomical correction of transposition of the great arteries in the first month of life. Postoperative peak flow velocities across the mitral valve and in the ascending aorta were not significantly different from those in an age matched control population, but tricuspid flow velocities were higher than normal. Aortic regurgitation was detected in only one of the eighteen patients, a markedly lower frequency than that reported after two stage anatomical correction. Peak velocities in the pulmonary artery were higher than normal, and in most cases there was some degree of stenosis of the pulmonary artery at the site of anastomosis.

Little is known of the haemodynamic results of neonatal anatomical correction of transposition of the great arteries. Doppler ultrasound has allowed detailed non-invasive assessment of haemodynamic function in older children after both the single stage and two stage operations for anatomical correction.^{1,2} This study was performed to assess the haemodynamic results of the arterial switch operation performed in the first month of life and to determine whether recognised complications, such as aortic regurgitation, could be avoided by early correction.

Patients and methods

Eighteen children who had undergone the arterial switch operation for complete transposition of the great arteries with intact ventricular septum between the ages of one and 31 days (mean (SD) 10 (8) days) were studied with pulsed and continuous wave Doppler ultrasound. In all cases the pulmonary artery anastomosis was direct and to the left of the aorta. The manoeuvre described by Lecompte *et al*³

was used in 15 children and in the remaining three anastomosis was possible without this procedure. The mean (SD) interval between operation and non-invasive investigation was 25 (14) months. The children constituted 64% of all those who had neonatal anatomical correction at Harefield Hospital up to the time of the study, and they were selected for investigation solely on grounds of their being able to attend at the time of the study.

Flow velocities were recorded distal to each of the four cardiac valves and, whenever possible, were also measured in the proximal branch pulmonary arteries. Peak flow velocities were measured for at least three cardiac cycles and the average of these values was recorded. Pressure drops, where appropriate, were calculated by the modified Bernoulli equation (by multiplying by four the difference between the squares of the velocities either side of an obstruction). The examination included systematic searching for regurgitant jets in both atria and both ventricular outflow tracts, as well as pulsed wave recordings of ascending aortic flow to detect any diastolic flow reversal caused by aortic regurgitation.^{4,5} We compared the results with those of 32 age matched normal children drawn from a large study of normal blood flow velocities.⁶

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STATISTICAL ANALYSIS

We used the Mann and Whitney U test to assess differences from the normal peak mitral, tricuspid, aortic, and pulmonary artery flow velocities because values in the postoperative patients were not normally distributed. We used Fisher's exact test to compare the frequency of aortic regurgitation in the present study population with that in an earlier study of children who had undergone two stage anatomical repair of complete transposition.²

Results

ATRIOVENTRICULAR FLOW VELOCITIES

Table 1 shows the peak flow velocities across the mitral and tricuspid valves. Flow velocities across the mitral valve were not significantly different from normal, but flows across the tricuspid valve were higher than normal. There was no significant relation between either peak mitral flow velocity and age or tricuspid flow velocity and age. No mitral regurgitation was detected, but in five patients there were low intensity tricuspid regurgitant signals that resembled those found in normal subjects.⁷

AORTIC FLOW VELOCITIES

Peak flow velocities in the ascending aorta (table 1) were slightly higher than those in the normal subjects, but this difference was not statistically significant. Aortic regurgitation was detected in only one (5.5%) of the children. This did not seem to be haemodynamically important because it did not produce any reversal of diastolic flow in the ascending aorta.

PULMONARY ARTERY FLOW VELOCITIES

The mean of the peak flow velocities in the main pulmonary artery was 2.9 m/s, equivalent to a peak pressure drop of approximately 34 mm Hg. Peak velocities were within 3 SD of the normal mean in only two children and the maximum calculated pressure drop in the main pulmonary artery was 185 mm Hg (table 2).

We were able to sample flow velocities distal to the bifurcation of the left pulmonary artery in five of the 18 children. In three there was an increase in velocity at the bifurcation caused by stenosis of the proximal branch (with calculated pressure drops of 24, 29, and 36 mm Hg). These three children had overall pressure drops between the right ventricular outflow tract and the left pulmonary artery of 36, 48, and 64 mm Hg respectively, indicating some degree of coexistent stenosis at the level of the anastomosis. The pulmonary arterial pressure drops in the remaining cases seemed to be solely at the anastomotic site. There was no relation between the

Table 1 Ages and peak blood flow velocities after the neonatal arterial switch operation and in the normal subjects

	After operation	Normal	p
No	18	32	
Mean (SD) age in years	2.1 (1.2)	2.2 (1.5)	NS
	Median (range) peak flow velocity in cm/s:		
Mitral	88 (62-117)	80 (48-124)	NS
Tricuspid	66 (48-103)	58 (41-114)	<0.04
Aorta	118 (70-260)	106 (73-155)	NS
Pulmonary artery	250 (120-680)	86 (56-119)	<0.001

Table 2 Peak flow velocities in the main and left branch pulmonary arteries

Case No	Peak flow velocity in cm/s	
	MPA	LPA
1	294	—
2	140	—
3	170	346
4	260	260
5	240	—
6	120	—
7	150	—
8	380	392
9	290	—
10	680	—
11	295	—
12	240	—
13	295	400
14	670	—
15	240	—
16	238	—
17	398	—
18	170	300
Median	250	—
Mean (SD)	293 (158)	—

Sampling of the left pulmonary artery was possible in only five children. MPA, main pulmonary artery; LPA, left pulmonary artery.

severity of pulmonary artery stenosis and the time since surgical correction. In seven children we detected weak signals of pulmonary regurgitation, like those seen in normal subjects.⁷

Discussion

ATRIOVENTRICULAR FLOW VELOCITIES

Anatomical correction by single stage operation in the neonatal period and later in life² is associated with normal peak mitral flow velocities. After the two stage operation, however, mitral flow velocities are increased, probably because of subtle abnormalities in left ventricular architecture.^{2,8-10} Tricuspid flow velocities were higher than normal both after two stage² and single stage repair, and it seems that these abnormalities (the importance of which is uncertain) are present even if correction is performed neonatally.

Table 3 Frequency of aortic regurgitation after neonatal anatomical correction and after two stage anatomical correction

Type of repair	Aortic regurgitation (%)	
	Present	Absent
Neonatal n = 18	1 (5.5)	17 (94.5)*
Two stage n = 18 ²	10 (55.5)	8 (44.5)*

*p < 0.002.

AORTIC FLOW VELOCITIES

Flow velocities in the ascending aorta are normal after the neonatal switch operation. This is in contrast with the two stage repair, after which they are significantly lower than normal, probably as a result of aortic root dilatation.² One of the most striking findings after neonatal correction was the low frequency of aortic regurgitation compared with the two stage anatomical repair (table 3). Trivial aortic regurgitation was detected in only 5.5% of children who had neonatal repair, whereas in an earlier study we found aortic regurgitation in 55% of patients after the two stage operation.² This result has implications for the aetiology of aortic regurgitation after the arterial switch operation. It has been suggested that pulmonary regurgitation may occur preoperatively in patients with complete transposition and that the posterior semilunar valve is inherently incompetent before correction in some patients.¹¹ The low frequency of aortic regurgitation after neonatal repair shown in this study, however, is conclusive evidence that the definitive aortic valve is potentially competent in nearly all cases. In terms of the risk of the development of aortic regurgitation, therefore, it seems better to perform anatomical correction in the neonatal period rather than later.

PULMONARY ARTERY FLOW VELOCITIES

Flow velocities in the pulmonary artery are almost invariably high after the neonatal switch operation, and there is important stenosis at the site of anastomosis in some children. Further stenosis at the origins of the branch pulmonary arteries was detected in three cases, and this feature may have been underestimated as it is technically difficult to ensure close alignment of the Doppler beam with the direction of blood flow in the branch pulmonary arteries. The findings in this study confirmed our previous experience that in some cases there is stenosis at the origin of the left pulmonary artery as well as main pulmonary artery stenosis. Although there can be pulmonary artery stenosis at the site of anastomosis after later single stage and two stage repair, in our experience obstruction at this level is more common and more severe after neonatal correction.

Neonatal anatomical correction of simple trans-

Gibbs, Qureshi, Martin, Wilson, Yacoub, Radley Smith

position of the great arteries gives better haemodynamic function of the aortic valve and avoids the abnormalities of left ventricular filling velocities seen after two stage repair. None the less, the high frequency of right ventricular outflow obstruction after neonatal correction remains a problem that requires further investigation and modification of surgical technique.

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Hypoplastic left heart syndrome and 45X karyotype

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SUMMARY A review of 63 patients with 45X karyotype (Turner's syndrome) admitted to a hospital from 1972 to 1985 showed that 20 (32%) had one or more major cardiac malformations (mostly coarctation and aortic stenosis). Four (20%) died in the neonatal period. One infant had mitral stenosis and severe aortic stenosis and died at the age of 35 days. The three (15%) other patients who died had a typical hypoplastic left heart syndrome, with an atretic aortic valve in two and pinpoint aortic valve in one. Turner's syndrome was clinically suspected in three of the cases. One of these had mosaicism (46XX,45X) the others had a 45X pattern. During the same period (1972-85) 39 patients (14 girls and 25 boys) were admitted with diagnosis of hypoplastic left heart syndrome. Three (21.4%) girls had a 45X karyotype. The high incidence of hypoplastic left heart syndrome in Turner's syndrome and of Turner's syndrome in girls with hypoplastic left heart syndrome suggests that hypoplastic left heart syndrome can be another expression of the 45X karyotype.

In 1938 Turner described a syndrome of infantilism, congenital webbed neck, and cubitus valgus.¹ It has been shown that gonadal dysgenesis is an almost invariable feature of this syndrome. Other frequent anomalies associated with this syndrome are small stature and lymphoedema of the extremities during the first year of life. In 1959 the first chromosome study showed that one X chromosome was absent in female patients with Turner's syndrome.² This discovery confirmed the earlier findings that many of these patients did not have sex chromatin in a smear of buccal cells. In addition to the absence of one X chromosome, which is the usual finding, various structural anomalies of the second X chromosome have been described.³ Many other congenital malformations have been reported in this condition.⁴ There are left sided congenital cardiac anomalies in 20%-40% of patients with Turner's syndrome.⁵⁻⁷ The most common is coarctation of the aorta. Less commonly reported are cases of isolated aortic stenosis, ventricular septal defect, atrial septal defect, subaortic stenosis, and idiopathic systemic hyperten-

sion. Isolated non-stenotic bicuspid aortic valve was found on echocardiography in 34% of the cases.⁸ Hypoplastic left heart syndrome had occasionally been reported with Turner's syndrome.^{9,10}

We reviewed a series of 63 patients with Turner's syndrome admitted to our hospital from 1972 to 1985. Twenty patients had one or more cardiac malformations (mostly coarctation and aortic stenosis), an incidence series in keeping with reported findings. Four (20%) of these patients died in the neonatal period. One patient showed moderate mitral stenosis and severe aortic stenosis; the other three had typical hypoplastic left heart syndrome.

Patients and methods

Between 1972 and 1985 four patients with Turner's syndrome died in the neonatal period of congenital heart disease. The table summarises data on their chromosomes and phenotypes. Typically, hypoplastic left heart syndrome caused cyanosis, tachycardia, tachypnoea, and heart failure. In two cases a heart murmur was noted and peripheral pulses were palpable in two cases. All cases had considerable oedema of the hands and feet. The diagnosis of hypoplastic left heart syndrome was confirmed by cardiac catheterisation in two cases; in the third case diagnosis was made by echocardiography only.

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Table Data on phenotype and chromosomes in four neonates with Turner's syndrome and hypoplastic left heart syndrome

Patient	Birthweight (g)	Ages at admission and death (days)	Phenotype	Necropsy data	Chromosomal analysis
1	3250	14, 41	Normal	Mitral stenosis, aortic stenosis, ductus arteriosus	45X
2	2700	15, 17	Pterygium colli, flat thorax, widely spaced nipples, oedema of hands and feet	Pinpoint aortic stenosis, hypoplastic left ventricle, rudimentary mitral valve, ductus arteriosus	45X
3	3100	1, 2	Typical facies, flat thorax, webbed neck, oedema of hands and feet	Aortic atresia, rudimentary mitral valve, ductus arteriosus	45% 45X 55% 46XX
4	2930	2, 3	Typical facies, webbed neck, flat thorax, widely spaced nipples, cubitus valgus, oedema of hands and feet	Aortic atresia, hypoplastic mitral valve, ductus arteriosus	45X

Results

FINDINGS AT NECROPSY

Case 1

This heart showed cardiomegaly caused by left ventricular enlargement, the cardiac apex being entirely made up of the tissue of the left chamber. When the heart was opened severe fibroelastosis of the endocardium was found to be especially widespread in the left ventricle. The oval foramen was small, functionally closed but probe patent. Examination of the right heart showed a normal atrium, ventricle, tricuspid valve, and pulmonary valve. The left atrium and auricle were dilated. There were multiple cysts of Lushka on the anterior cusp of the mitral valve. The papillary muscles were fibrotic and the chordae tendineae were shortened. The left ventricle was hypertrophic, with a bicuspid and stenotic aortic valve (diameter 3.2 mm compared with 10.5 mm for the pulmonary valve). The ascending aorta and the pulmonary trunk were dilated. The ductus arteriosus was probe patent and fibrotic.

The diagnosis was bicuspid and stenotic aortic valve with hypertrophy and enlarged (fibroelastosis) left heart with a relatively small but probe-patent oval foramen.

Case 2

The right atrial appendage was enlarged. The diameter of the oval foramen was small but it admitted a probe. The tricuspid valve, right ventricle, and pulmonary valve were normal. There was a non-obstructive rim between the pulmonary veins and the bottom of the left atrium. The mitral valve was very small (diameter 1.3 mm). The wall of the left ventricle was made up of hyperplastic muscular tissue. The aortic valve (diameter 1.0 mm) and the ascending aorta were hypoplastic. The aortic arch was interrupted between the left carotid artery and the left subclavian artery. The right and the left subclavian arteries originated from the descending

aorta. The large diameter ductus was functionally and anatomically patent. Unusually there was a median artery between the two carotid arteries. It bifurcated after 5 mm. This was taken to be remnants of the anterior aorta and both first aortic arches, which normally regress.

The diagnosis was left heart hypoplasia, rudimentary mitral valve, extremely hypoplastic left ventricle and ascending aorta, pinpoint aortic valve, interruption of the aortic arch, aberrant right subclavian artery, and a small probe-patent oval foramen.

Case 3

The right atrium and auricle were dilated and enlarged. The tricuspid valve, the right ventricle, and the pulmonary valve were normal. The left atrium and left auricle were small and there was a type II atrial septal defect. The mitral valve and the left ventricle were rudimentary and the aortic valve was atretic. A large open ductus arteriosus connected a narrow ascending aorta with the pulmonary trunk. The diagnosis was left heart hypoplasia, rudimentary mitral valve and left ventricle, and atresia of the aortic valve.

Case 4

Both atria and a small left ventricle were located behind an anterior right ventricle. The right atrium and auricle were enlarged. Both the tricuspid valve and the right ventricle were normal. The oval foramen was covered by a membrane with two small openings. The left atrium and auricle were normal. The mitral valve (4 mm), the left ventricle (6 mm), and the ascending aorta were hypoplastic and the aortic valve was atretic. Inspection of the vascular tree showed a dilated pulmonary trunk, a widely patent ductus arteriosus, and an aberrant right subclavian artery. The diagnosis was left heart hypoplasia, aortic atresia, and considerable hypoplasia of the left ventricle, ascending aorta, and mitral valve, with an aberrant right subclavian artery and a type II atrial septal defect.

Discussion

In three of these four cases of Turner's syndrome a 45X karyotype was suspected on clinical grounds. All three had hypoplastic left heart syndrome. In the fourth case clinical examination was normal and moderate mitral stenosis and severe aortic stenosis were found at necropsy. One patient had mosaicism (45X, 46XX karyotype) and the other three had a 45X karyotype.

In the same period (1972–85) we examined 39 (14 girls and 25 boys) patients with hypoplastic left heart syndrome. Thirteen of the girls had chromosomal analysis: three (21%) had a 45X karyotype (one mosaicism 45X, 46X) and in the others the chromosomal pattern was normal.

In a series of 1498 aborted fetuses with hypoplastic left heart syndrome chromosomal analysis showed the 45X karyotype in 18.7%.¹¹ A high lethality is unusual in X linked anomalies, where the clinical expression of the anomaly is high, and the lethal effect is much less than in autosomal aneuploidy.¹² The flow theory postulates that coarctation is the result of left ventricular obstructive disease in the fetus that reduces the flow through the ascending aorta and the aortic arch and increases the flow through the pulmonary artery truncus.¹³ Because many patients with Turner's syndrome and cardiac disease have coarctation and aortic stenosis a form of left obstructive disease would be expected in utero. Hypoplastic left heart syndrome is a severe left sided obstructive disease and it could be one of the causes of the high incidence of intrauterine death in patients with Turner's syndrome—only one out of 300 45X conceptuses survived to birth.¹⁴ A study of the cardiovascular system and chromosomal typing in aborted fetuses is needed to investigate this suggestion.

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Clinical implications of atrial isomerism

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SUMMARY Right atrial isomerism or left atrial isomerism is frequently diagnosed as situs ambiguous without further discrimination of the specific morbid anatomy. Thirty six cases of right atrial isomerism and seven cases of left atrial isomerism were collected from the records and pathological museum at the National Taiwan University Hospital. There was a necropsy report for 18 cases. In all patients one or more of the following conditions was met: (a) isomeric bronchial anatomy, (b) echocardiographic and angiographic evidence of isomerism, and (c) surgical or necropsy evidence of abnormal atrial anatomy. An anomalous pulmonary venous connection was present in 55% of patients with right atrial isomerism; in left atrial isomerism one case (14%) had a partial anomalous pulmonary venous connection. Forty per cent of cases of anomalous pulmonary venous connection with right atrial isomerism had obstruction. Six (86%) of seven cases with left atrial isomerism had an ambiguous biventricular atrioventricular connection. In contrast, univentricular atrioventricular connection (26 of 36, 72%) was significantly more common in right atrial isomerism. A common atrioventricular valve was the most frequent mode of connection in both forms. Two discrete atrioventricular valves were significantly more common in left atrial isomerism. Atrioventricular valve regurgitation was detected in 14 cases. Double outlet right ventricle was the most common type of ventriculoarterial connection. The most commonly cited causes of death after either palliative or definitive operation were undetected anomalous pulmonary venous connection, pulmonary venous stricture, and uncorrected atrioventricular valve or aortic regurgitation complicated by abnormal coagulation.

Although the prognosis is poor, successful operation depends on knowledge of the precise anatomical arrangement associated with atrial isomerism.

Complex congenital heart disease is known to be combined frequently with visceral heterotaxia,^{1,2} and until recently the emphasis has been on arrangement of abdominal organs and presence or absence of spleen.¹⁻⁶ The concept of asplenia and polysplenia syndromes in association with bilateral right sidedness and left sidedness has led to great confusion and misunderstanding. It is recognised that there is less discord between the arrangement of atria and thoracic organs than that between atria and abdominal organs.^{7,8} The pattern of lung lobulation is less accurate than the bronchial arrangement in predicting atrial situs.^{7,8} Thus right atrial isomerism is not always associated with asplenia nor left atrial isomerism with polysplenia.

We have studied patients with atrial isomerism in our hospital to get a better understanding of the anatomical arrangement, so that operations may be better planned.

Patients and methods

We reviewed the records of paediatric and surgical patients at the National Taiwan University Hospital from November 1983 to November 1986 and all the available heart specimens in the pathology department. Every study patient met one or more of the following criteria: (a) isomeric bronchial anatomy shown by penetrating chest radiographs or high kilovoltage filter film; (b) echocardiographic and angiographic evidence of atrial isomerism; and (c) surgical or necropsy evidence of atrial morphology. Cross sectional echocardiography was performed in 33 patients. There were 18 necropsy specimens. All chest radiographs and angiograms

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were reviewed. We studied the position of the heart and its apex; the air-bronchogram; anomalies of systemic and pulmonary venous connection, atrioventricular connection, and ventriculoarterial connection; and the presence or absence of Howell-Jolly bodies. The criterion for establishing right atrial isomerism is the presence of bilateral triangular right atrial appendages or early branching of the bronchus.^{7,8} In left atrial isomerism there are bilateral slender left atrial appendages or hypoarterial and longer bronchi. We used methods of sequential segmental analysis and nomenclature used elsewhere.^{7,9} The statistical significance of the differences between two groups was evaluated by a Fischer's exact test. In all analyses, the 95% confidence level was regarded as significant.

Results

There were seven cases (4 female, 3 male) of left atrial isomerism and 36 cases of right atrial isomerism (15 female and 21 male).



Fig 1 Anomalous left upper pulmonary vein (white arrow head) draining into left superior vena cava (star) in a case of right atrial isomerism with modified Blalock-Taussig shunt (arrow).

SYSTEMIC VENOUS CONNECTION

Interruption of inferior vena cava was seen in four (59%) cases of left atrial isomerism. Bilateral inferior vena cava was found in two cases of right atrial isomerism. Sixteen cases (44%) of right isomerism had bilateral superior vena cava. In 20 with single superior vena cava the vein was right sided in 13 and left sided in seven.

PULMONARY VENOUS CONNECTION

One partial anomalous pulmonary venous connection (14%) was found in left atrial isomerism. In patients with right atrial isomerism, eight (22%) had partial anomalous pulmonary venous connection and 12 (33%) had total anomalous pulmonary venous connection. A left upper pulmonary vein draining into left superior vena cava was most frequently seen in partial anomalous pulmonary venous connection (fig 1). In one case the right upper pulmonary vein was hypoplastic and a membrane covered the orifice of right lower pulmonary vein at its entry into the right sided morphologically right atrium (fig 2a). Oedema developed in the right upper lung field after a modified Blalock-Taussig Shunt (fig 2b). Total anomalous extracardiac connection was to the superior vena cava in three, to an infradiaphragmatic channel in three, and in two cases it was of a mixed type. The other five cases of total anomalous pulmonary venous connection drained to the heart through a narrow channel of pulmonary venous confluence (fig 3). In one case of total anomalous pulmonary venous connection the ascending vein was trapped inside the lung parenchyma and drained to the superior vena cava, which was obstructed by a stricture. There was clinically significant obstruction in eight (40%) of the 20 cases of partial or total anomalous pulmonary venous connection with right atrial isomerism.

ATRIAL SEPTUM

A common atrium was found in 29 cases: four with left isomerism and 25 with right isomerism. A strand of atrial septal remnant was the most common feature. If present the oval fossa located in the superior rim of atrial septum was hypoplastic. In one case of right atrial isomerism unroofing of coronary sinus had produced a small interatrial communication. A sinus septum (left venous valve or septum spurium) was the only intra-atrial septum present in three cases of right atrial isomerism.

ATRIOVENTRICULAR CONNECTION (TABLE 1)

In atrial isomerism the biventricular atrioventricular connection is neither concordant nor discordant. It is ambiguous. A biventricular and ambiguous connection was common in left atrial isomerism (86%), whereas a univentricular atrioventricular connection

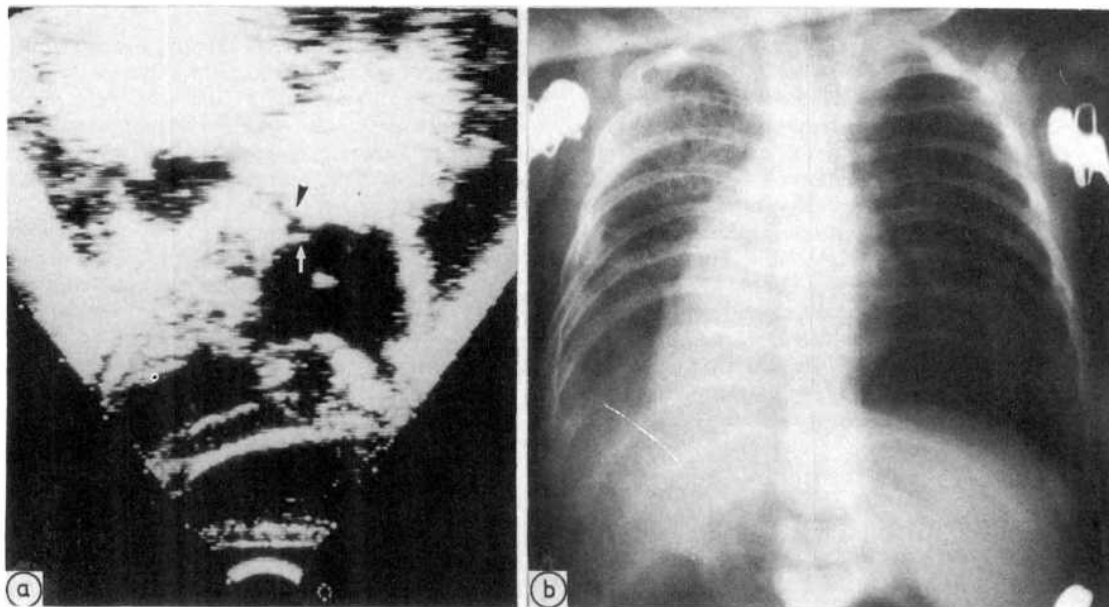


Fig 2 (a) Echocardiogram of a hypoplastic right upper pulmonary vein (black arrow head) in a case of right atrial isomerism. The entry site of right upper pulmonary vein is partially obstructed by a membrane (arrow). (b) Chest x ray showing lung oedema in the right upper lung field after a modified Blalock-Taussig shunt.

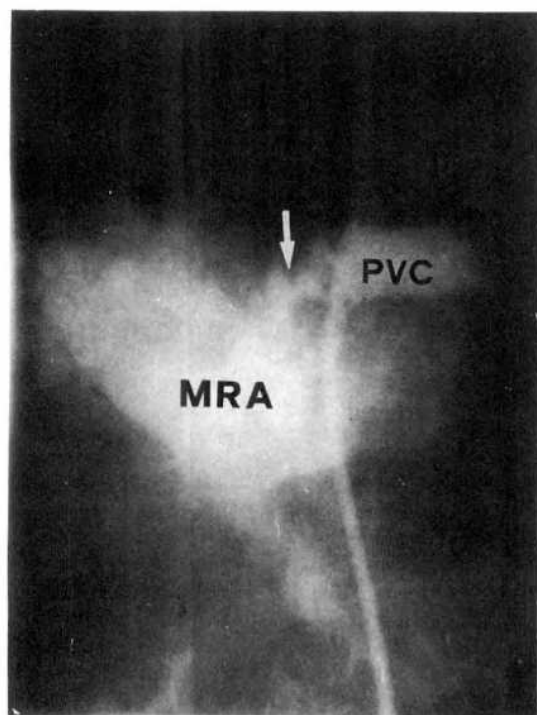


Fig 3 Angiogram showing the pulmonary venous confluence (PVC) draining into the morphologically right atrium (MRA) through a narrow channel (arrow) in a case of right atrial isomerism. This patient survived the Fontan operation after relief of pulmonary venous obstruction.

was common in right atrial isomerism (72%) ($p < 0.005$) (table 1). There was a common atrioventricular valve in 36 (84%) of the 43 cases. None of the cases with univentricular atrioventricular connections had two atrioventricular valves. Two discrete atrioventricular valves were present in four of seven cases with left atrial isomerism. This feature was less common in right atrial isomerism (three (9%) of 36) ($p < 0.005$). There was atrioventricular valve regurgitation in four cases of left atrial isomerism and 10 cases of right atrial isomerism. Valvar regurgitation was more frequent with a common atrioventricular valve than two atrioventricular valves (NS).

VENTRICULOARTERIAL CONNECTION

Discordant connection and double outlet right ventricle were common in right atrial isomerism (table 2). There was pulmonary obstruction in 29 (81%)

Table 1 Type and mode of atrioventricular connection in 43 patients with atrial isomerism

Isomerism		Ambiguous biventricular	Univentricular		
			Left	Right	Indeterminate
Left	7	6	1	0	0
Right	36	10	11	14	1
n = 43		2 valve	1 valve	2 valve	1 valve
Left	7	4 (2)*	2 (2)*	0	1
Right	36	3	7 (4)*	0	26 (6)*

*Regurgitation.

Table 2 Type of ventriculoarterial connection in 43 patients with atrial isomerism

Isomerism (n = 43)		Concordant		Discordant		DORV		DOV		Single	
AV connection		B	U	B	U	B	U	B	U	B	U
Left	7	2	0	0	0	4	0	0	0	0	1
Right	36	0	0	1	9	4	12	0	1	5	4

B, biventricular; DORV, double outlet right ventricle; DOV, double outlet ventricle; U, univentricular.

cases of right atrial isomerism and five (71%) cases of left atrial isomerism. Nine (25%) cases of right atrial isomerism and one (14%) of left atrial isomerism had pulmonary atresia.

CARDIAC POSITION AND DIRECTION OF THE APEX

The cardiac apex was directed to the left in five (71%) cases of left atrial isomerism and in 26 (72%) cases of right atrial isomerism. It was directed to the right in nine (25%) cases of right atrial isomerism and in two (29%) cases of left atrial isomerism. One case of right atrial isomerism had a midline heart with the apex directed to the middle.

BRONCHIAL ARRANGEMENT

The bronchial arrangement was determined by x ray and necropsy (if available) in 34 patients. In nine patients radiographs were unsatisfactory and there was no necropsy report. There was no discord between the atrial situs and the bronchial arrangement.

ARRANGEMENT OF THE ABDOMINAL ORGANS

Normal arrangement (solitus) was found in three patients with right atrial isomerism and mirror image arrangement (inversus), in two with right atrial isomerism, and in one with left atrial isomerism. The remaining cases had heterotaxy. Two cases of hiatus hernia and one case of inguinal hernia were associated with right atrial isomerism. Omphalocele was found in one case of left atrial isomerism. A Howell-Jolly body was not found in seven (19%) cases of right atrial isomerism.

SURVIVAL IN THE UNOPERATED GROUP

No operation was performed for cardiac anomalies in 10 patients with right atrial isomerism and three with left atrial isomerism. Two patients with right atrial isomerism aged 2 months and 6 years and two with left atrial isomerism aged 3 and 8 months were known to be alive at the end of November 1986. Their age was 2 month and 6 year respectively. The mean (SE) age at death in eight unoperated cases of right atrial isomerism was 80 (44) days. The surviving patients are either awaiting a suitable time for operation or are not suitable for operation.

SURGERY AND ITS RESULTS

Thirty patients were referred for cardiovascular surgery—26 with right atrial isomerism and four with left atrial isomerism. One patient with left atrial isomerism died after omphalocele repair. Ten patients with right atrial isomerism had systemic to pulmonary shunts (Blalock-Taussig, Gortex shunt, or central shunt); six died (60%). Two patients with left atrial isomerism and a Gortex shunt have survived. Seven patients with right atrial isomerism and one patient with left atrial isomerism had a Fontan operation; only one patient survived. Pulmonary artery banding was attempted in three patients with right isomerism; all of them died. Two patients with right atrial isomerism had atrioventricular valve replacement for regurgitation; one survived. The other case of right atrial isomerism survived the repair of an unroofed coronary sinus. Two patients underwent cardiopulmonary bypass to correct total anomalous pulmonary venous connection; both died. One patient each in two groups had a Rastelli operation; both died.

CAUSES OF DEATH AFTER SURGERY (TABLES 3 AND 4)

The main causes of death after Fontan operation (table 3) were consequences of residual anomalous pulmonary venous connections, atrioventricular valve regurgitation, aortic regurgitation, or a ductus arteriosus, which resulted in cardiac failure. A bleeding complication occurred in two patients within a week of a Fontan operation although the central venous pressure was maintained around 18 mm Hg. Anomalous pulmonary venous connection could be

Table 3 Causes of death after Fontan operation (n = 7)

Cause	No
Sepsis	1
PAPVC	2
Coagulopathy*	2
Residual ASD	1
Pump failure	1

*One patient also had aortic regurgitation.

ASD, atrial septal defect; PAPVC, partial anomalous pulmonary venous connection.

Table 4 Causes of death after shunt operation (n = 6)

Cause	No
PAPVC	1
TAPVC	3
Pulmonary vein stricture and PAPVC	1
Shunt obliterated plus PAPVC	1

PAPVC, partial anomalous pulmonary venous connection,
TAPVC, total anomalous pulmonary venous connection

seen in all patients who died after shunt operation (table 4).

Discussion

Right atrial isomerism is characterised by bilateral triangular, morphologically right atrial, appendages, both joining the atrial chamber along a broad front with internal terminal crest. In left atrial isomerism there is a bilateral small finger-shaped morphologically left atrial appendage joining the atrial chamber along a narrow front without an internal terminal crest.⁷ In life atrial situs is best diagnosed by examination of bronchial anatomy on a high kilovoltage filter chest radiograph.^{8,10} Like Deanfield *et al* we found that an anteroposterior view gave the most informative air bronchogram.⁸ Examination at operation and necropsy in our series confirmed that there was no discord between the atrial situs and the bronchial situs, although others have reported inappropriate bronchial arrangements.^{8,11} The absence of spleen in so-called asplenia syndrome should invariably be accompanied by a Howell-Jolly body, but this was not present in 19% of our patients with right atrial isomerism. Use of the Howell-Jolly body as a diagnostic predictor for right atrial isomerism would have missed a fifth of these cases.

Echocardiography of the abdominal great vessels and hepatic venous drainage are diagnostically more accurate than an assessment of the abdominal organs.^{11,12} One of our patients with right atrial isomerism, however, had the usual arrangement of both abdominal organs and great vessels.

As in other clinical and pathological series we found that the pulmonary venous connection was abnormal in 55% of patients with right atrial isomerism.¹¹ The high frequency (97%) of anomalous pulmonary venous connection in necropsy series⁷ may be because those cases that come to necropsy die of severe associated abnormality. The poor results of definitive surgery or palliative shunts in our series may be related to the presence of anomalous pulmonary venous connection. In a recent series from

Brompton Hospital 10 patients with right isomerism had shunts; seven died.¹¹ Although the cause of death was not stated, these results suggest that babies with right atrial isomerism were too ill to stand even a shunt procedure. One factor may be that increased pulmonary blood flow through the shunt flooded the lung with pulmonary venous obstruction. Cross sectional echocardiography is the most informative investigation for anomalous pulmonary venous connection in right atrial isomerism.¹³ Preoperative evaluation in patients with right atrial isomerism can be difficult because there are two morphologically right lungs which considerably reduce the size of the precordial echo-window.¹¹ In such cases, it is important to check the pulmonary venous drainage of upper lobe on both sides during operation. Sometimes the drainage orifice of middle lobe only is mistaken for the drainage orifice of both upper and middle lobes of bilateral right lungs. In our series two consecutive cases of anomalous pulmonary venous connection in which the left upper pulmonary vein ran into the left superior vena cava were not detected until necropsy.

Why is anomalous pulmonary venous connection so common in right atrial isomerism? The morphologically right atrium might reject the entry of pulmonary veins during embryogenesis, or the pulmonary veins might lose their ability to recognise and connect with the morphologically right atrial chamber. These two mechanisms could account for total anomalous pulmonary venous connection, partial anomalous pulmonary venous connection, hypoplastic pulmonary vein, and pulmonary venous confluence with a narrow entry into the atrial roof as found in almost all the patients with right atrial isomerism. The same mechanisms could account for the arrangement of the suprarenal portion of the inferior vena cava in left atrial isomerism. This could explain why an interrupted inferior vena cava was so common in our cases (57%) and those reported by others (64%).⁷ The high incidence (39–64%) of partial anomalous pulmonary venous connection in left atrial isomerism in published reports^{2,7,11,14} could be explained by recognition of pulmonary vein by the ipsilateral morphologically left atrium producing a bilateral connection. For the same reason the inferior vena cava might connect with the ipsilateral morphologically right atrium and produce bilateral inferior caval veins as we found in two cases of right atrial isomerism. This speculation is contradicted by the frequency of total anomalous pulmonary venous connection in left atrial isomerism (0–13%),^{11,14} which is much lower than its occurrence in right atrial isomerism (38–97%).^{2,7,11} An interrupted inferior vena cava is sporadically reported in right atrial isomerism.¹¹

One of our cases of left atrial isomerism had omphalocele. Two cases of right isomerism had hiatus hernia and one inguinal hernia. The relevance of these abnormalities is unknown. Left atrial isomerism was less common in our series than in other series.¹¹⁻¹⁵ This might be because associated malformations are often less severe in this condition and would not lead to referral to a regional centre. So far the results of operation in babies and children with right atrial isomerism with anomalous pulmonary venous connection are not encouraging. The precise identification of the anatomical abnormality in cases of the atrial isomerism is a prerequisite for successful operation.

We thank Professor and Chairman Kai-Mo Chen, Department of Surgery, College of Medicine, National Taiwan University, for his constant support of our study and for revision of the paper.

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Case reports

Infective endarteritis affecting the left pulmonary artery after anatomical correction of complete transposition of the great arteries

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SUMMARY Clinical features of infective endocarditis developed in a two year old boy. He had successfully undergone anatomical correction of complete transposition of the great arteries during the neonatal period. At routine investigation one year later he showed evidence of important supravulvar pulmonary stenosis. He remained symptom free until endocarditis developed. *Streptococcus pneumoniae* was isolated from serial blood cultures. Despite prompt treatment with specific intravenous antibiotic treatment the patient died of overwhelming sepsis. At necropsy the stenosed portion of the left pulmonary artery was seen to be the site of infection.

Although anatomical correction for complete transposition of the great arteries was first described over ten years ago the operation is still a comparatively new procedure.¹⁻³ There is much interest in the long term follow up of patients undergoing this operation. Supravulvar pulmonary stenosis appears to be an important finding.^{4,5} Infective endocarditis, however, is a complication that has not previously been reported.

We describe a fatal case of fulminating infection that occurred at the site of supravulvar pulmonary stenosis after this operation.

Case report

A two year boy was admitted to hospital after a short history of fever and non-specific malaise. As a neonate he had undergone anatomical correction of complete simple transposition of the great arteries. The pulmonary artery was reconstructed by the method described by Lecompte *et al.*⁶ Dura was used to repair the defects left in the pulmonary trunk after the transfer of the coronary arteries.

There were no operative or early postoperative complications and he was routinely investigated when he was 14 months old. Cardiac catheterisation showed the presence of considerable supravulvar

pulmonary stenosis with pressure drop on withdrawal of 75 mm Hg and simultaneous right and left ventricular systolic pressures of 95 mm Hg and 80 mm Hg respectively. A right ventricular angiogram (fig 1) showed severe narrowing of the distal pulmonary trunk extending into the left proximal pulmonary artery. Because he was symptom free with good right ventricular function non-urgent surgical repair of the pulmonary stenosis was planned. He remained symptom free until three weeks before admission. His initial symptoms were attributed to a possible infection of the upper respiratory tract for which his general practitioner prescribed a week's course of antibiotics. Because there was no clinical improvement he was admitted to hospital.

He had a fever (38°C). He appeared clinically anaemic and was peripherally cyanosed with cool extremities. He had a sinus tachycardia and clinical evidence of right ventricular hypertrophy. There was a systolic thrill and grade 4/6 ejection murmur that was loudest over the left second intercostal space. There were no other abnormal findings.

The initial chest x ray was normal. Cross sectional echocardiography confirmed the presence of right ventricular hypertrophy with severe supravulvar pulmonary stenosis. It did not show any evidence of infective vegetations. His haemoglobin was 7.7 mg/l with a hypochromic microcytic blood film. He had a leucocytosis of $18.5 \times 10^6/l$ (predominantly neutro-

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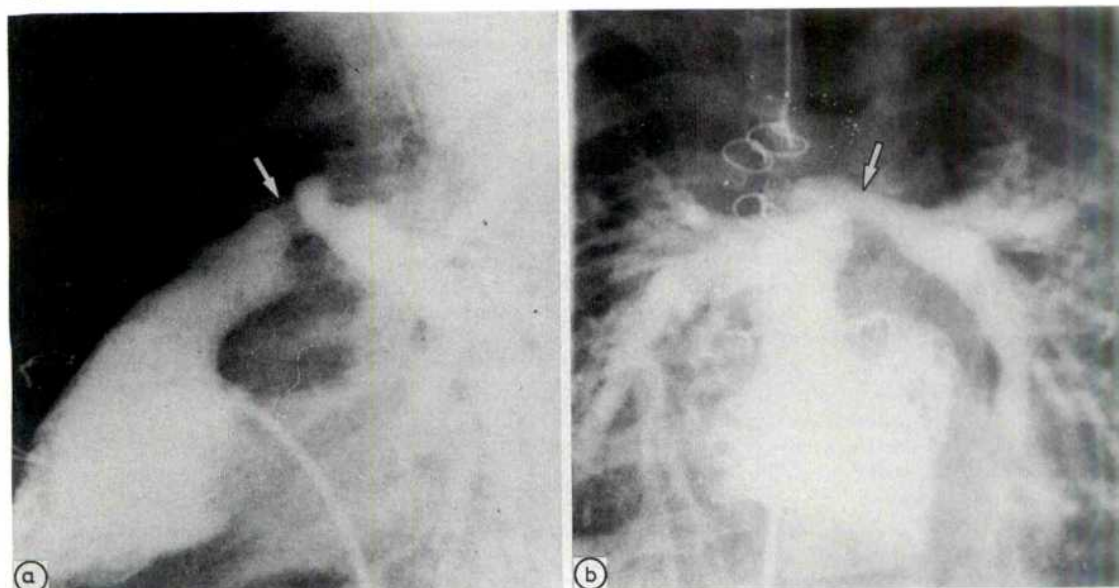


Fig 1 Right ventricular angiograms in anteroposterior (a) and lateral projections (b) showing supavalvar stenosis in the main pulmonary trunk and in the left branch pulmonary artery (arrows).

phils). Infective endocarditis was considered the likely diagnosis and serial blood cultures were taken. After 48 hours these grew *Streptococcus pneumoniae* and treatment with intravenous benzyl penicillin (50 mg/kg, four hourly) was started immediately. A few hours later presumed septicaemic shock developed and he suffered an asystolic cardiac arrest, from which he was resuscitated. He became oliguric and uraemic with signs of disseminated intravascular coagulopathy. He developed acute renal failure,

requiring peritoneal dialysis. Three days later he remained febrile with a persistent leucocytosis. Repeated blood cultures were all negative.

In view of persisting sepsis and his deteriorating condition he was treated with a broad spectrum antibiotic (cefuroxime 100 mg/kg/24 h) on the second day. Aminoglycosides were avoided because of his renal failure. An indium-111 (fig 2) labelled white cell radionuclide scan showed a possible area of increased uptake in the region of the pulmonary trunk. The child's condition deteriorated rapidly and he died before any surgical intervention could be performed. Necropsy showed a hypertrophied right ventricle with a healthy pulmonary valve. The main pulmonary trunk was stenosed and the narrowing extended into the left pulmonary artery. Infective vegetations occluded the left pulmonary artery.

Discussion

The risk of infective endocarditis is considerably increased in children with congenital heart disease, and the disease can occur with almost any lesion.⁷ Surgical repair, both palliative and corrective, can affect the subsequent risk of developing infective endocarditis.^{8,9} We identified supavalvar pulmonary stenosis as an important complication after anatomical correction for complete transposition of the great arteries; it was more common when the operation was performed in the neonatal period.^{4,5} Turbulent blood flow distal to the stenotic lesion may

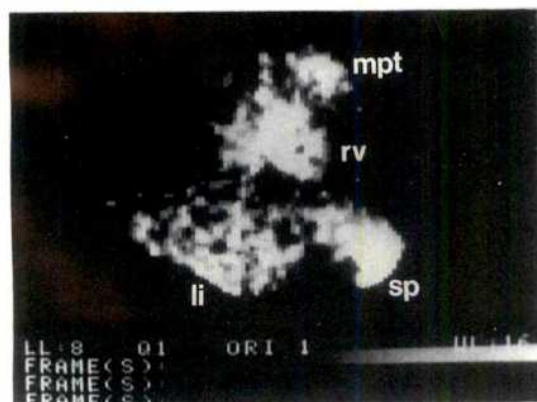


Fig 2 An indium-111 labelled white cell radionuclide scan showing an area of increased uptake representing the heart (right ventricle, rv) which extends into the region of the main pulmonary trunk (mpt). The liver (li) and spleen (sp) can be seen below the diaphragm.

increase the risk of developing infective endarteritis.

Rodbard first described how endocarditis tends to occur at sites where blood flow velocity is high.¹⁰ This may be because excessive flow causes a venturi effect, creating a distal area of low pressure and perfusion. The intima is also damaged in these areas, and both factors may make the region more susceptible to colonisation by pathogens. Endocarditis affecting the right side of the heart is otherwise uncommon in children, with the exception of infections of the conduits connecting the right atrium to pulmonary artery.

The site of infection was not firmly diagnosed during the patient's illness. Cross sectional echocardiography is often useful in demonstrating the presence and position of infective vegetations¹¹ but in this case the vegetations were not visualised. This may reflect the relative difficulty of imaging infective vegetations in an already irregular and stenosed pulmonary trunk. The indium-111 labelled white cell radionuclide scan was performed in the presence of persisting sepsis with a view to eliminating additional sites of infection.¹² The result was of value in localising the infection to the heart and excluding the presence of intracerebral and intraabdominal infection. There was increased uptake in the region of the ventricular mass extending to the pulmonary trunk. Indium-111 labelled white cell radionuclide imaging, therefore, could potentially be of value in localising infections of the distal pulmonary trunk.

The commonest organisms isolated from patients with infective endocarditis are the *Streptococcus viridans* group, which account for 50% of all culture positive cases.¹³ Endocarditis caused by *Streptococcus pneumoniae* is uncommon. In normal hearts it can occur as a complication of lobar pneumonia or meningitis and has been recognised in children with right atrial isomerism and asplenia syndrome.¹⁴ We know of no specific reasons why this patient was infected with this organism because we could not identify the portal of entry.

Once he was admitted to hospital the infective endocarditis was quickly diagnosed and appropriate treatment was started. Despite this the infection could not be adequately controlled. Operation was considered but the development of rapidly deteriorating cardiac and renal function precluded this. Earlier referral to hospital might have improved the outcome. It is possible that early correction of supravulvar pulmonary stenosis could prevent this serious complication. Technical modifications of the operation may also help by reducing the incidence of supravulvar pulmonary stenosis.

Infective endocarditis may develop after anatomical correction for complete transposition of the great arteries. The possibility of infection within

the pulmonary trunk should be considered. We hope that an awareness of this complication will help in its prevention and treatment.

We thank Professor M H Yacoub for allowing us to report on one of his patients.

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Coronary artery-right ventricular fistula after endomyocardial biopsy

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SUMMARY A coronary artery-right ventricular fistula developed after endomyocardial biopsy in a recipient of an orthotopic cardiac transplant.

The technique of percutaneous transvenous endomyocardial biopsy of orthotopic cardiac grafts was developed in 1971 in the laboratory and was clinically applied the next year at Stanford University.¹ Biopsy is performed by cannulation of the right internal jugular vein and passage of the biopsy forceps through a sheath into the right ventricle under fluoroscopic control. Because it is a safe procedure endomyocardial biopsy can be performed as often as indicated, and this permits the diagnosis of rejection before graft damage becomes irreversible.

Case report

A 44 year old woman underwent orthotopic cardiac transplantation for congestive cardiomyopathy in August 1986. Appendicectomy for acute appendicitis was performed on the tenth postoperative day. She was discharged on the twenty second postoperative day and remained symptom free until October 1986. Then she became breathless on exertion, and orthopnoea and ankle swelling developed. On examination she had a raised jugular venous impulse, hepatomegaly, ankle oedema, and a third heart sound. Chest x ray showed bilateral pleural effusions. An endomyocardial biopsy specimen showed moderate rejection with myocyte necrosis. She was treated with a rapidly tapering dose of oral prednisolone. Follow up endomyocardial biopsy specimens confirmed the resolution of this episode of rejection but her congestive cardiac failure did not improve. Investigation including echocardiography was suggestive of either pericardial constriction or myocardial restriction.

The myocardium seemed to be abnormally echogenic and there was global left ventricular dysfunction. In December 1986 cardiac catheterisation confirmed the presence of pericardial fluid and a constrictive/restrictive pattern with reduced ventricular function.

Selective injection of the left coronary artery showed dye entering the right ventricle (figure).

A decision was made to retransplant the patient. Her degree of heart failure worsened while she was waiting for a suitable donor. By the time of emergency retransplantation in February 1987 legionella peritonitis and pneumonia had developed. She died of cerebral haemorrhage secondary to disseminated intravascular coagulation caused by the uncontrolled septicaemia. Postmortem injection of the coronary arteries was not performed and the fistula was not demonstrated in the excised heart.

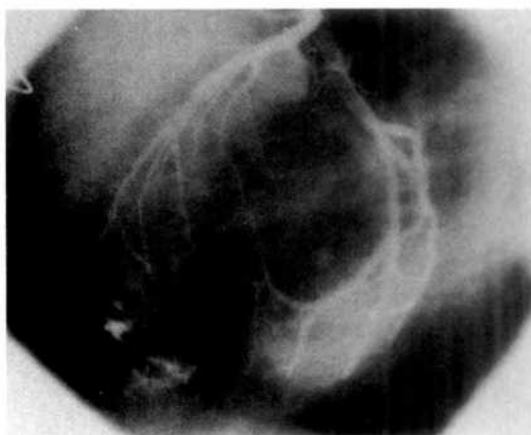


Figure Selective injection of left coronary artery showing leakage of dye from the distal vessel into the right ventricular cavity.

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Discussion

Endomyocardial biopsy remains the reference standard for the diagnosis of cardiac allograft rejection. Although much effort has been directed to the search for non-invasive methods of diagnosis of rejection, none has yet replaced histological examination of biopsy material. With care, the risk of endomyocardial biopsy to the patient is minimal.

At Stanford University, 10 000 endomyocardial biopsies have been performed with no mortality. Cardiac perforation has developed in three of the heart transplant recipients from whom biopsy specimens have been taken (M E Billingham, personal communication).

Our case represents a previously unreported complication of endomyocardial biopsy. In the Freeman Hospital 400 biopsies have been performed in 28

cardiac transplant recipients. This is the only case of morbidity associated with biopsy. The fistula was not clinically important and was asymptomatic. The fistula must have been created when a biopsy specimen was taken from the junction of the right ventricular free wall and the septum—the point at which the left anterior descending artery lies closest to the right ventricular cavity. This report emphasises that the biopsy specimens of the endomyocardium should not be taken from the apex of the right ventricle.

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Angina pectoris treated by ventricular plication

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SUMMARY Objective analysis of the left ventricular angiogram in a patient with angina but normal coronary arteries showed an appreciable disturbance of regional wall movement. Because of persistent symptoms refractory to medical treatment left ventricular plication was undertaken. This resulted in a return to normal of a series of disturbances of left ventricular wall motion commonly found in patients with obstructive coronary disease, and a striking improvement in the patient's symptoms. The patient remains symptom free five years after operation.

It is well recognised that typical angina can occur when coronary arteriography is entirely normal, though in some patients abnormal left ventricular wall movement can be demonstrated by objective analysis of cineangiograms. We have previously argued that regional abnormalities of diastolic wall movement may interfere with coronary blood flow and so be the direct cause of anginal pain.¹ Ventricular surgery, by modifying the pattern of wall movement, might thus be beneficial when intractable angina proves resistant to conventional medical treatment.

We report a patient with normal coronary arteries and abnormal left ventricular wall movement, in whom the chest pain resolved, exercise tolerance increased, and regional left ventricular wall motion was strikingly improved after left ventricular plication. He remains symptom free five years after operation.

Case report

A 59 year old civil servant was admitted to his local hospital in January 1978 with a three year history of exertional chest pain and dyspnoea, with a severe episode on the day of admission. Myocardial infarction was diagnosed on the basis of raised concentrations of cardiac enzymes, though the electrocardiogram, which showed sinus rhythm, a normal QRS axis, and right bundle branch block, did not change. He made an uneventful recovery and was discharged, but subsequently he was referred to this hospital because of continuing exertional chest pain and dyspnoea.

There was no relevant past or family history. He had stopped smoking 80 cigarettes per day four years before. Clinical examination was unremarkable apart from a corneal arcus and wide splitting of the second heart sound because of right bundle branch block. Chest x ray and routine haematology and biochemistry were normal apart from a slight increase in the concentration of fasting serum cholesterol (7.8 mmol/l). Selective coronary arteriography was normal and left ventricular end diastolic pressure was 14 mm Hg. Objective angiographic analysis is discussed below.

The patient continued to have disabling chest pain on exertion and dyspnoea over the next few years despite numerous adjustments to his drug treatment. These episodes of pain resulted in several admissions to hospital, but there was never any change in the electrocardiogram or cardiac enzymes. Because of the strong clinical impression of angina the patient had two further coronary arteriograms over the next three years. Both of these were normal and left ventricular wall movement on cineangiography was the same as before. Formal exercise testing was performed on two occasions according to the standard Bruce protocol with the patient being limited by chest pain and dyspnoea. Interpretation of ST segment changes was complicated by the presence of right bundle branch block. The mean rate-pressure product at maximum exercise was 15 950 mm Hg/min. Echocardiography, 24 hour ambulatory electrocardiographic recording, and respiratory function tests were unremarkable.

For reasons to be discussed, left ventricular apical plication was advised. At operation (MP) in April 1982 the external appearances of the left ventricle were normal. On full cardiopulmonary bypass a left ventricular vent was inserted via the apex of the left ventricle, and the apex, including its posterior and

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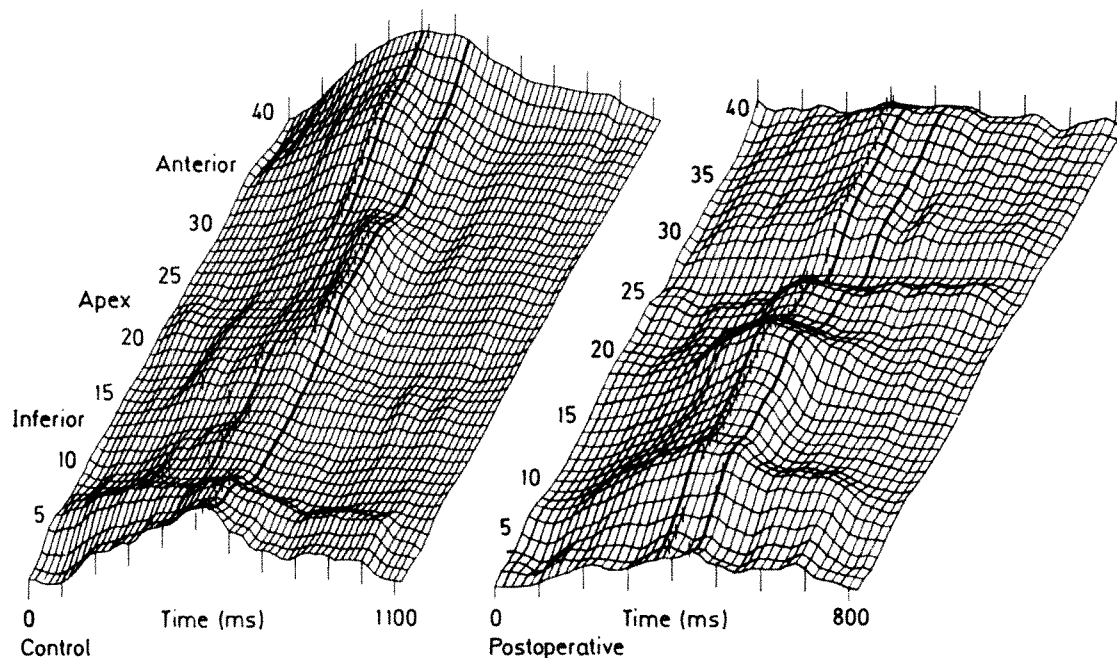


Fig 1 Preoperative "control" and postoperative plots of left ventricular regional wall movement against time. Each horizontal line represents wall motion at one of 40 points around the perimeter of the cavity and the diagonal lines are isochrones connecting simultaneous events. The two accentuated isochrones are the times of minimum cavity area and mitral valve opening.

anterior walls, was plicated with mattress sutures of Ethibond tied over a U-shaped strip of Teflon felt. The heart was then defibrillated, the vent removed, and the site oversewn.

The patient's postoperative recovery was unremarkable and in five years of follow up he has been well with only very occasional episodes of left sided chest pain, considerable improvement in dyspnoea, and an increased exercise tolerance. Formal exercise testing has been performed twice since the operation and on both occasions this was limited by fatigue and the patient had no chest pain. The mean rate-pressure product at peak exercise was 28 860 mm Hg/min.

ANALYSIS OF LEFT VENTRICULAR ANGIOGRAMS

The method underlying angiographic analysis² is designed to display regional wall motion around the cavity outline throughout the cardiac cycle so that disturbances in the timing as well as the amplitude of regional wall motion can be studied and compared with normal results.³ The plots of regional wall motion (fig 1) continuously display the movement of each of forty points around the left ventricular cavity perimeter throughout the cardiac cycle. The same information can be presented as a contour display (fig 2). Each contour line represents 1 mm inward or

outward motion of endocardium from its position in the end diastolic (maximum volume) frame and shows the timing of such movement in relation to minimum cavity area and mitral valve opening.

The plots derived from the preoperative angiogram (November 1981) demonstrate an abnormal reduction in the overall amplitude of inward motion along the inferior wall ≤ 4 mm. On the anterior wall (segments 20–30) the onset of inward motion at the start of ejection was delayed by more than 100 ms, and this led to a characteristic pattern of "diagonal contours". In the same segments during the isovolumic relaxation period between minimum cavity area and mitral opening there was abnormal inward motion of endocardium by 4 mm, representing a significant change in left ventricular cavity shape. The preoperative ejection fraction was 0.70.

The postoperative left ventricular angiogram (January 1983) showed major alterations from the preoperative pattern of regional wall motion. There was localised hypokinesia in segments 25–28, corresponding to the area plicated at operation, but the overall amplitude of left ventricular wall motion was normal along the entire inferior wall. In addition, the timing of wall motion was also normal. The onset of inward motion around the left ventricular cavity outline occurred within a period of 100 ms and the

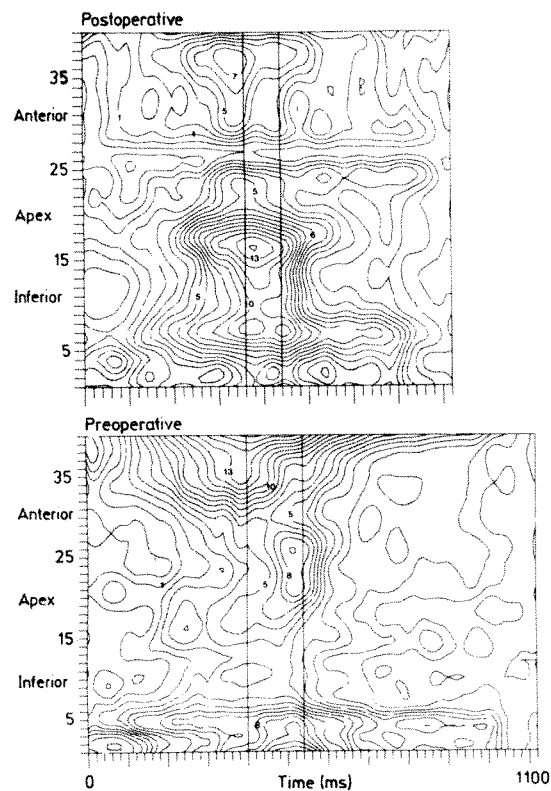


Fig 2 Preoperative and postoperative plots for the same data as fig 1 with left ventricular wall movement displayed as contours joining points moving in 1 mm increments from their position at maximum cavity area. The accentuated vertical lines are minimum cavity area and mitral valve opening.

disturbance of wall motion during isovolumic relaxation was no longer apparent. The ejection fraction (0.65) remained normal.

Discussion

The present case showed many of the familiar clinical features of the syndrome of chest pain with a normal coronary arteriogram. The patient required frequent admissions to hospital with episodes of chest pain that were believed to have been ischaemic in origin and there was objective limitation of exercise tolerance in terms of exercise load and rate-pressure product. Despite this, coronary arteriography was normal on three occasions. Arteriography was repeated because of the strong clinical impression that there must be an objective abnormality to account for the patient's severe and predictable limitation of exercise tolerance.

Although the large and medium sized coronary

arteries were normal, the left ventriculogram showed several specific abnormalities, all of which may occur in patients with obstructive coronary artery disease. There was a major abnormality in the timing of wall motion during isovolumic relaxation that affected the free wall.² In patients with single vessel disease this disturbance typically occurs in the territory supplied by the affected coronary artery and causes a characteristic change in ventricular cavity shape during the isovolumic period, with complementary outward motion elsewhere, usually along the upper part of the free wall as in the present case.² Delay in the onset of inward wall motion at the start of ejection is also seen in patients with coronary artery disease under control conditions. Such regions are commonly the site of more pronounced disturbances of wall motion occurring during pacing induced angina,⁴ and in single vessel disease they again occur in the territory of the affected coronary artery.

Abnormal regional wall motion during isovolumic relaxation might of itself interfere with regional perfusion. Prolongation of local systole leads to a reduction in the time available for coronary flow, and in particular to loss of perfusion during the early diastolic period when coronary flow is usually rapid.⁵ Local ischaemia, once established, would be expected to cause further prolongation of systole and interference with relaxation, thus making the disturbance self-perpetuating and possibly explaining development of rest pain.

In view of these considerations, and of the manifest failure of medical treatment to control this patient's symptoms, we felt that operation was justified. After operation there was a striking improvement in symptoms with an increase in exercise tolerance and an 80% rise in rate-pressure product on exercise testing. It is now more than five years since operation and this improvement has been maintained.

The present case raises several questions. The patient had typical angina and detailed angiographic analysis showed at least three features commonly seen in patients with coronary artery disease, although coronary arteriography was normal. Coronary artery spasm is often invoked as an explanation, but it is difficult to see why any primary disturbance of coronary vasomotion should be so completely suppressed by localised plication of ventricular myocardium. A striking feature was the extent to which a widespread series of disturbances in regional left ventricular wall motion were reversed after local surgery. It would not have been unexpected for the abnormality of isovolumic relaxation to have been abolished, since the site of the plication itself was selected as that of the abnormal inward movement. More surprising is the reversion to normal of the preoperative inferior wall hypokinesia

(an observation that excludes death of the myocardium as the basis for this abnormality) and the timing of onset of inward left ventricular wall motion around the cavity outline. An intervention designed to modify motion in a very localised region and at a specific time in the cardiac cycle has thus been shown to lead to an improvement that was very much greater in extent, both spatially and temporally. If the reverse can occur in disease it suggests that abnormalities of wall movement, particularly those in its timing, may be involved in the genesis of angina in patients with uncomplicated coronary artery disease and that investigation of such abnormalities should be pursued in more detail than before. Indeed, many current approaches to angiographic analysis such as the two-frame or "center line" methods take no account of asynchrony at all.⁶ Detailed analysis of regional wall motion might also be fruitful in other conditions associated with angina and normal coronary arteriograms, such as left ventricular hypertrophy. Regional delay in the onset of inward motion at the start of ejection has already been reported in patients with hypertrophic cardiomyopathy.⁷

Finally, the present case raises the possibility that a direct surgical approach to abnormalities of regional wall motion may be of clinical value in some patients whose coronary artery disease is either too mild or too severe to justify conventional coronary artery surgery. If such direct left ventricular surgery is to develop fruitfully, however, it must be based on a more extensive understanding of the interrelations

between regional structure and function than is currently available.

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A progressive pericardial effusion caused by psittacosis

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SUMMARY A patient developed signs of a progressive pericardial effusion over a period of eight days. Diagnostic and therapeutic pericardiocentesis was performed. Viral titres to psittacosis rose from < 1:8 to > 1:256 indicating recent infection.

Chlamydial infections produce a wide variety of clinical problems but rarely affect the heart.¹ We describe a case of acute pericarditis caused by psittacosis in which a large pericardial effusion required pericardiocentesis.

Case report

In a 55 year old woman a central constricting chest pain developed and became worse over two days. It was associated with dry cough and breathlessness. There was no past history of heart disease. She was taking thyroxine (200 µg daily) for longstanding primary hypothyroidism and prednisolone (5 mg daily) for late onset asthma. She smoked 20 cigarettes per day.

On examination she looked flushed but was otherwise well. Her temperature was 38°C, her pulse was 86 per minute and regular, and her blood pressure was 160/90 mm Hg. The jugular venous pressure was not raised and the heart sounds were normal. No friction rub was heard. Chest examination revealed an expiratory wheeze and the peak expiratory flow rate was 270 l/min.

The white cell count was $13.7 \times 10^9/l$ (79% neutrophils) and the erythrocyte sedimentation rate was 68 mm/h (Westergren). Cardiac enzymes, the electrocardiograph, and chest radiograph were normal. Eighteen hours after admission left anterior pleuropericardial pain and atrial fibrillation developed. Examination of the arterial blood gases showed pH 7.438 (normal range 7.35-7.45), partial pressure of oxygen (P_{O_2}) 11.1 kPa (normal range 12-15 kPa), partial pressure of carbon dioxide (P_{CO_2}) 4.63 kPa (normal range 4.5-6.0 kPa) on air. An electrocardiogram confirmed atrial fibrillation but

was otherwise unchanged, and the chest radiograph remained normal. Pulmonary embolism was suspected and treatment with heparin (15 000 units twice daily) was started. Twelve hours later a further electrocardiograph showed sinus rhythm with atrial supraventricular extrasystoles and concave upward ST elevation in both the anterior and inferior leads. Anticoagulation was stopped because of suspected pericarditis. A repeat chest radiograph showed no change of heart size.

Three days after admission she developed further pain, rapid atrial fibrillation and the blood pressure fell to 90/60 mm Hg. A pericardial friction rub was heard at the left sternal edge. A chest radiograph now showed an increase in the size of the cardiac silhouette and a left basal pleural effusion. Cross sectional echocardiography confirmed a pericardial effusion and showed a cystic lesion in the region of the posterior tricuspid valve leaflet (fig 1). Antinuclear antibodies and anticardiac antibodies were negative; serum viral titres for Coxsackie B1-B6, influenza A+B, mumps, and psittacosis/lymphogranuloma venereum were all < 1:8. A Mantoux reaction was positive at a 1:1000 dilution.

She improved after treatment with digoxin, indomethacin (50 mg three times daily), and erythromycin (500 mg four times a day). Sinus rhythm was restored, blood pressure rose, and she had less pain. An intermittent fever (up to 38.5°C) persisted.

During the next week the size of the pericardial effusion increased considerably on the chest radiograph (fig 2) and cross sectional echocardiograph. The jugular venous pressure rose to 9 cm and the blood pressure averaged 100/70 mm Hg. Diagnostic and therapeutic pericardiocentesis was performed because of the signs of progressive subacute tamponade. We withdrew 500 ml of blood stained pericardial fluid. Microbiological studies of the fluid including examination for acid and alcohol

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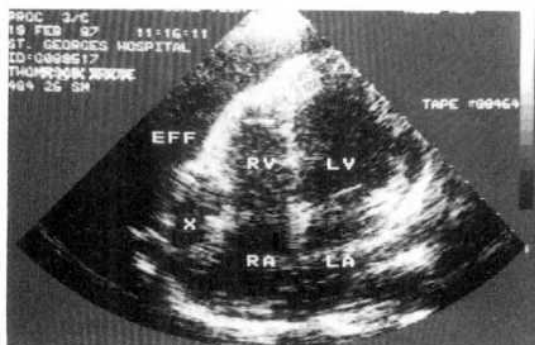


Fig 1 Cross sectional echocardiograph performed three days after admission. EFF, effusion; X, cystic lesion; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

fast bacilli as well as cytological examination were negative. After the procedure the cystic lesion was no longer visible on cross sectional echocardiographs.

Fifteen days after admission the titre of antibody to psittacosis/lymphogranuloma venereum measured by complement fixation and immunofluorescence techniques rose to $>1:256$ from the initial value of $<1:8$. Oxytetracycline (500 mg four times daily) was started. The temperature became normal over five days and the left basal pleural effusion disappeared over two weeks.

A one month course of treatment was planned, but after three weeks the pericardial and pleural effusions and the chest pain recurred. The effusions resolved within one week with bed rest and indomethacin (500 mg four times daily). Oxytetracycline was continued for two months in total. No further relapses occurred during four months of follow up and the

chest radiograph and electrocardiograph became normal. The psittacosis/lymphogranuloma venereum titre fell to 1:8.

On enquiry the patient reported brief exposure to a parrot two weeks before admission. The owner refused to let us investigate the bird.

Discussion

Acute *Chlamydia psittaci* infection is usually transmitted by inhalation of the dried excreta of psittacine birds and in most cases produces a respiratory illness. The diagnosis is by serology, and an antibody titre of 1:16 to the group specific antigen of the psittacosis/lymphogranuloma venereum group is regarded as positive.² Cardiac involvement is rare and often complicates psittacosis related respiratory disease.³ Both endocarditis^{4,5} and myocarditis^{6,7} have been reported and the small number of necropsy reports show endocardial involvement as the major pathological feature.¹ We found only three reported cases of documented pericardial effusion caused by psittacosis.^{1,8} To our knowledge this is the first reported case of the development of a large pericardial effusion requiring pericardiocentesis after psittacosis. The rise and fall of the antibody titre to the *Chlamydiaceae* group specific antigen was considerable and there were no features of ocular or genital disease or cat scratch fever to suggest *Chlamydia trachomatis* infection, which is a cause of false positive results.⁹ The lungs were only slightly affected; she had a dry cough at presentation and a small left sided pleural effusion developed. The response to standard antibiotics was slow but this was a feature of the case reported by Kundu and Scott⁸ and may reflect the difficulty in

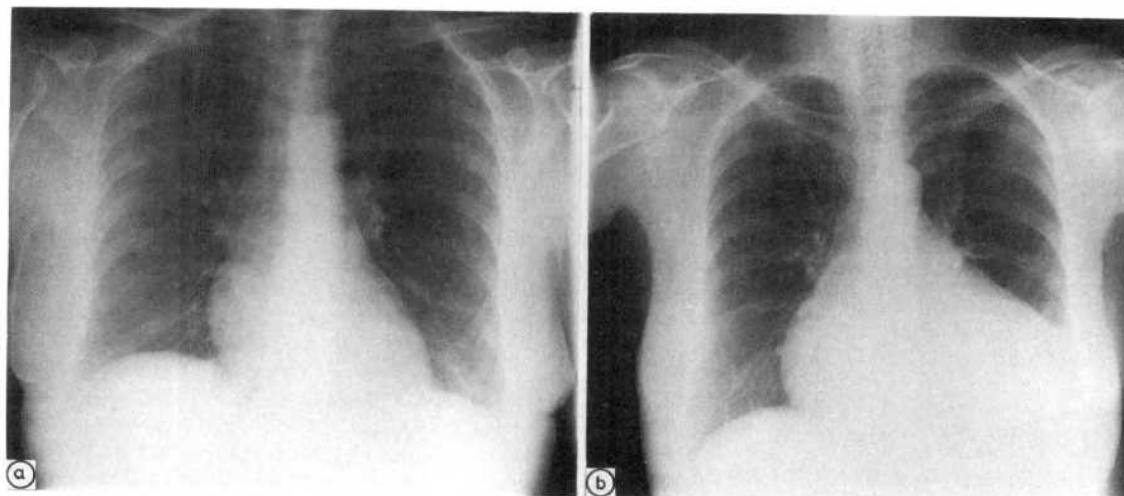


Fig 2 Chest radiographs taken on admission (a) and nine days after admission (b).

eradicating the organism from the pericardial effusion.

Sutton *et al.*, in a review of 599 unselected cases of acute pericarditis, found nine cases with serological evidence of psittacosis, with pericardial effusions in two.³ In four cases heart disease was the only clinical manifestation. In six patients the diagnosis was by serology, with an antibody titre > 1:32. No titres > 1:16 were recorded in a control population of 1000. Five patients recovered completely but their treatment regimens were not reported.

The nature of the cystic lesion seen on initial echocardiography remains uncertain. It most probably represents encysted pericardial fluid and rupture during pericardiocentesis may account for its disappearance.

It is often difficult to obtain an accurate history of bird exposure in psittacosis.¹⁰ In the present case the history of exposure was obtained only after serological diagnosis. We therefore recommend the measurement of antibody titres of psittacosis/lymphogranuloma venereum titres in all cases of acute pericarditis regardless of pulmonary involvement. If the diagnosis is confirmed treatment with oxytetracycline should be continued for at least two months.

We thank Professor J S Jenkins for permission to report this case and to Mr G Leach for the echocardiography.

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Anomalous origin of the left anterior descending coronary artery from the pulmonary trunk: recognition in life and successful surgical treatment

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SUMMARY An anomalous origin of the left anterior descending coronary artery from the pulmonary trunk with the right and left circumflex arteries arising from the aorta is very rare and the diagnosis made only at necropsy. An anomalous coronary artery was suspected owing to unexplained cardiomegaly in a 17 month old girl and the anatomy was defined by angiography. The anomalous vessel was successfully reimplanted into the aorta.

Anomalies of origin of the coronary arteries are uncommon. Anomalous origin of only the left anterior descending coronary artery from the pulmonary trunk has been reported in eight cases (seven adults and one infant). We describe the first case of this condition diagnosed and treated successfully by operation in early childhood.

Case report

A 17 month old symptom free girl was referred from Qatar because of unexplained cardiomegaly detected by routine chest radiography after a chest infection. She was a well-built (10.95 kg), healthy child. Arterial and venous pulses were normal and blood pressure was 105/70 mm Hg. The left ventricle was enlarged. The second sound was reversed and there was an apical late systolic murmur and a soft short ejection murmur at the upper left sternal border.

Investigations confirmed thalassaemia major with haemoglobin concentration of 123 g/l. An electrocardiogram recorded three weeks before referral (fig 1) showed evidence of left ventricular hypertrophy and anterolateral myocardial infarction—that is Q waves and ST segment elevation in leads I, aVL, V5, and V6; and T wave inversion in V1-4. A later electrocardiogram showed depression and sharp T inversion in the same leads. Cross sectional echocardiography showed that the left ventricle was dilated and the lateral wall moved poorly. The ejection fraction was 0.29. The right and left coronary arteries seemed to

arise from the right and left aortic sinuses respectively (fig 2). Doppler echocardiography detected mild mitral regurgitation. The activity of cardiac enzymes was increased (creatinine kinase 79 IU/l,

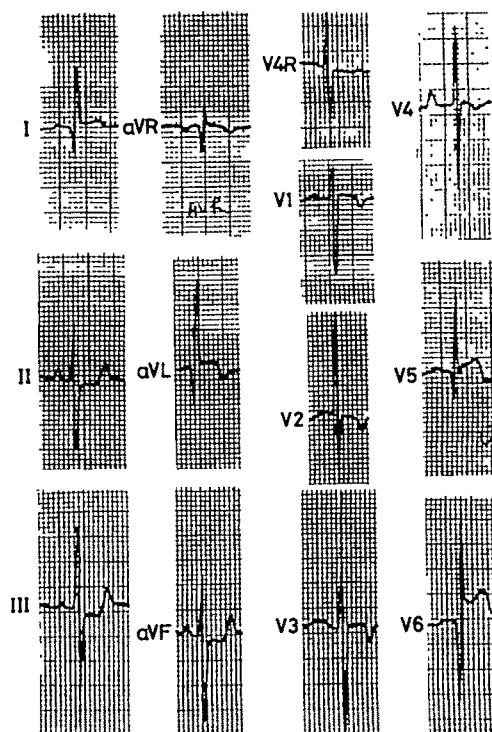


Fig 1 Electrocardiogram showing anterolateral myocardial infarction, ST elevation, and deep Q waves in leads I, aVL, and V5-6, with reciprocal ST depression in leads II, III, and aVF.

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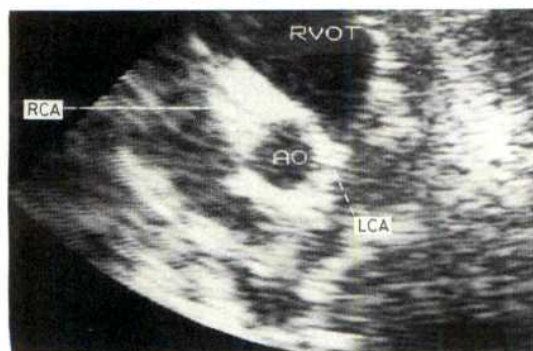


Fig 2 Cross sectional echocardiogram, short axis view above the level of the aortic valve, showing normal origin of the right and left coronary arteries. AO, aorta; LCA, left coronary artery; RCA right coronary artery; RVOT, right ventricular outflow tract.

creatinase kinase MB 35 IU/l, and hydroxybutyrate dehydrogenase 262 IU/l).

The clinical diagnosis was that of anomalous left coronary artery with anterolateral myocardial infarction. Pressures measured at cardiac catheterisation were: left ventricle 100/18 mm Hg and pulmonary trunk 36/22 mm Hg. There was no increase in oxygen saturation in the pulmonary artery. Angiography of the left ventricle showed a dilated chamber with a hypokinetic anterolateral wall. The results of angiography of the right ventricle were normal. Aortic root angiography showed that the right coronary artery was larger than the left coronary artery and that both arose from the usual coronary sinuses. Careful re-examination of the angiogram showed that the left anterior descending coronary artery appeared to fill slightly later than the left coronary artery via scanty collaterals from the right coronary artery; it ascended to empty at a level higher than the origin of the small left coronary artery. Flash opacification of the pulmonary arteries was detected on late pictures.

Anomalous origin of the left anterior descending coronary artery from the pulmonary trunk was diagnosed. Surgical reimplantation of the vessel into the aorta was recommended.

At operation the left anterior descending coronary artery was seen to have a normal diameter and arose from the right posterior sinus of the pulmonary trunk. There was a whitish discoloration of the anterior wall of the left ventricle which was dilated and poorly contracting. The origin of the left anterior descending coronary artery was taken from the pulmonary artery with a cuff of arterial wall. The vessel was dissected to give enough length to reach the left posterior aspect of the ascending aorta and an anastomosis was constructed.

Two weeks after operation, the chest x ray showed

some cardiomegaly and the electrocardiogram showed left axis deviation, isoelectric ST segments with deep Q waves in lead I, aVL, V5, and V6, and upright T waves in V1-4. Cross sectional echocardiography showed improved left ventricular function, an ejection fraction of 0.40, with improved, but still abnormal, motion of the lateral wall of the left ventricle. Doppler echocardiography showed that mitral regurgitation was reduced. The activity of the cardiac enzymes was normal. The patient left hospital three weeks later and has remained symptom free and normally active.

Six months later she was well and active. Chest x ray showed that there had been a further reduction of the heart size, but some cardiomegaly remained, and the electrocardiogram showed a normal axis and deep Q waves in leads I and aVL. Cross sectional echocardiography showed improved left ventricular function, an ejection fraction of 0.45, with more improvement in motion of the lateral wall of the left ventricle, but this was still abnormal. Doppler echocardiography showed trivial mitral regurgitation.

Discussion

When a child of less than two presents with unexplained left ventricular failure or hypertrophy the possibility of an anomalous origin of a coronary artery must be considered. In this case, the presence of an electrocardiographic pattern of myocardial infarction was highly suggestive of the diagnosis and for this reason the anomaly was specifically sought.

Cross sectional echocardiography is unreliable for making the diagnosis because two coronary arteries often appear to arise from the root of the aorta. The presence of a segmental area of hypokinesia is suggestive of a localised problem rather than a cardiomyopathy. Angiography of the aortic root or coronary vessels is the most certain method of diagnosis. In this case only the left anterior descending coronary artery was anomalous, and we were temporarily deflected from the correct diagnosis when we saw that the origins of the right and left coronary arteries were normal.

We decided to operate because there was a possibility that the infarction was relatively recent, had come on slowly without symptoms, and that some of the left ventricular dysfunction was recoverable. We hoped for a long term improvement. In the early postoperative period the left ventricular ejection fraction increased, and within six months the heart had become smaller.

Schwartz and Robicsek reported a seven month old female infant who presented with heart failure.¹ Her electrocardiogram showed myocardial ischaemia

and she had cardiomegaly on the chest x ray and a normal origin of a small left coronary artery.

Schwartz and Robicsek believed that this was a hypoplastic left coronary artery that was causing ischaemia. The patient later died from acute myocardial infarction and the diagnosis was made at necropsy. The high origin of the left anterior anomalous descending coronary artery had been noted but its significance was not appreciated.

Seven adults aged 18–55 years have been reported; only one case was male. Angina that required investigation by coronary angiography drew attention to the anomaly.^{2,4} One case presented with fatigue which was attributed to severe mitral regurgitation caused by papillary muscle dysfunction.⁵ Another case was symptom free and attention was drawn to the abnormality by a continuous murmur.⁶ Three patients aged 45, 18, and 55 years had cardiomegaly.^{4,7} The pattern of anterolateral ischaemia, but not infarction, was shown on the electrocardiogram. Two cases had normal electrocardiograms.^{3,5} Several surgical treatments have been described and three out of seven patients were alive after 12, 25, and five months.^{3,4,7} Although patients survive to adulthood without symptoms, we consider that when the anomaly is identified in childhood it should be corrected in the hope of preventing damage to the left ventricle.

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Notice

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 22 to 24 November 1988. The closing date for receipt of abstracts was 24 June 1988.

The Annual General Meeting for 1989 will take place in Oxford on 6 and 7 April 1989, and the closing date for receipt of abstracts will be 6 January 1989.

Correspondence

Latent pre-excitation: exposure of anterograde accessory pathway conduction during atrial fibrillation

Sir,

Robinson *et al* (1988;59:53-5) have described three patients with "latent pre-excitation".¹ During sinus rhythm there was no delta wave, whereas during atrial fibrillation there apparently was considerable pre-excitation. All three cases had a left lateral accessory pathway. It is therefore quite understandable for Robinson *et al* to seek to explain this interesting phenomenon in terms of the location of the accessory bundle.

Milstein *et al*² have recently reported that patients with the Wolff-Parkinson-White syndrome and those with enhanced conduction in the atrioventricular node who were matched for anterograde refractory period showed similar ventricular rates during atrial fibrillation. They had expected a slower ventricular response when conduction through the atrioventricular node was enhanced because of a greater propensity for concealed conduction. We found^{3,4} that all anterograde conduction was blocked when patients with atrial fibrillation had right ventricular pacing at intervals that were twice as long as the shortest RR intervals without such pacing.

Comparative studies of the mammalian atrioventricular conduction system⁵⁻⁷ show a mismatch between heart size and atrioventricular conduction time, with small mammals having relatively long PR intervals and large mammals relatively short atrioventricular transmission times. Both observations led us to question⁸ the traditional concepts of atrioventricular conductivity—that is that the atrial impulse is conducted slowly through the atrioventricular node and at high speed through the His-Purkinje system to the ventricles.

We cannot be certain who introduced the concept of atrioventricular conduction.⁹ Certainly, nobody has ever proved that the atrial impulse that leaves the atrioventricular node is the same one that enters it. We suggested that continuous overdrive suppression of the automaticity of the atrioventricular node may explain anterograde block during right ventricular pacing and atrial fibrillation.⁴ In other words, during atrial fibrillation (without right ventricular pacing) there may be no atrioventricular conduction, but rather automaticity of the atrioventricular node and random electrotonic modulation of phase 4 of the

atrioventricular nodal pacemaker.¹⁰ If automaticity of the atrioventricular node can undergo overdrive suppression by retrogradely conducted ventricular impulses, in principle impulses reaching the atrioventricular node from the atrial direction could have the same effect. Atrioventricular transmission during sinus rhythm would then not be caused by actual conduction of the atrial impulse through the atrioventricular node and the His-Purkinje system, but by a continuous resetting of the pacemaker of the atrioventricular node entrainment by the successive atrial excitation waves, followed by conduction through the His-Purkinje system.¹¹ Concealed conduction of atrial extrasystoles can be explained on the basis of hyperpolarisation of the pacemaker cell during phase 4 of the monophasic action potential. Overdrive suppression and resetting of the pacemaker of the atrioventricular node does not need to take much more time in large atrioventricular nodes than in the smaller ones. This may explain the relatively short PR intervals in the larger mammals.⁶

The enhanced atrioventricular conduction described by Milstein *et al*² could be caused by enhanced automaticity of the pacemaker of the atrioventricular node, for whatever reason; this would be hard to modulate by atrial fibrillation. The propensity for concealed conduction during atrial fibrillation, according to our theory, depends on the rate of rise of phase 4 depolarisation of this suggested atrioventricular pacemaker and the capacity of the atrial impulses that reach the atrioventricular node to modulate this depolarisation. So in patients with accessory pathways and atrial fibrillation transmission of the atrial impulses by the accessory pathway rather than by the normal atrioventricular transmission system would also depend on the rate of rise of diastolic depolarisation of the pacemaker of the atrioventricular node. From the moment impulse propagation occurs via the accessory pathways during atrial fibrillation, it is quite likely that concealed retrograde overdrive suppression of automaticity may take place, sealing off the atrioventricular node from atrial impulses. This explanation does not take into account the left sided location of the accessory bundle. The left sided site only explains the lack of

pre-excitation during sinus rhythm, not the preference for the bypass tract during atrial fibrillation.

Thus latent pre-excitation could become apparent during atrial fibrillation if the atrioventricular node is an unprotected pacemaker that exhibits resetting during sinus rhythm and electrotonic modulation during atrial fibrillation.

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This letter was shown to one of the authors, who replies as follows:

Sir,

We were aware of the interesting concepts developed by Meijler and his colleagues which have recently been published. Their attractive hypothesis can be tested and potentially falsified, and time will tell whether it will replace current views on atrioventricular conduction.

Meijler questions these classic concepts and wonders how they were developed. There was much debate on this question at the turn of the century¹; and when Mackenzie formulated his ideas on the clinical aspects of conduction of the atrial impulse to the ventricles he based them substantially on the fundamental work of Gaskell, Keith, and Kent in England and on the observations of Engelmann of Utrecht and Wenckebach, then of Groningen.² The following year Tawara described the atrioventricular node,³ and in the first edition of Mackenzie's *Diseases of the heart*, figure 2 shows "the Knoten of Tawara"; the novel concept that conduction occurred through the atrioventricular node was considered at some length.⁴

Whether the physiological concept of atrioventricular node conduction is correct, or whether Meijler's attractive hypothesis achieves acceptance, the factors that we described in our patients with latent pre-excitation presumably caused the latent accessory pathway to become activated during atrial fibrillation while the function of the atrioventricular node was depressed. What we saw in our patients is not incompatible with the new hypothesis.

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British Heart Journal

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Editorial

Ischaemic ventricular aneurysms: true or false?

M J DAVIES

From the British Heart Foundation Cardiovascular Pathology Unit, St George's Hospital Medical School, London

Left ventricular aneurysm is a common complication of acute myocardial infarction. The reported incidence ranges from 4%, if the definition is restricted to a localised protrusion of the external aspect of the left ventricle, to 40%, if localised akinesia or dyskinesia during systole is the criterion.¹ It has become a common clinical practice to classify ventricular aneurysms with an external bulge as true or false.^{2,3} The wall of the true aneurysm is derived from the myocardium itself whereas the wall of the false aneurysm (pseudoaneurysm) is derived from the pericardium (figure). The pseudoaneurysm is thought to be the result of a "near miss" myocardial rupture during an acute infarct with the formation of a subpericardial haematoma.⁴⁻⁶ An acute pericarditis develops and fibrous thickening of the pericardium encompasses the haematoma, ultimately forming the free wall of a sac that connects by a narrow aperture with the left ventricular cavity. The designation of true or false applies solely to the postulated origin of the wall of the sac; both are aneurysms as defined as an external bulge filled with pulsating blood.

Although pseudoaneurysms were first described at necropsy, this approach cannot either establish the frequency of pseudoaneurysms in living patients or define the risk of rupture. Basic principles suggest that the risk that a haematoma retained only by the visceral pericardium will rupture fatally within a day or two must be very high; long term survival with the formation of a pseudoaneurysm would accordingly be rare.

Two series composed of nine pathologically proven cases of pseudoaneurysm, in which echocardiography had been carried out in life, laid down criteria for the diagnosis.^{2,7} The diagnostic echocardiographic features were that the maximal internal diameter of the neck (O max) was less than the

maximal parallel internal diameter of the sac (D max) and that the ratio O max/D max never exceeded 0.5. The ratio for true aneurysms was > 1.

A paper in this issue of the *British Heart Journal*⁸ challenges the view that pseudoaneurysms can be diagnosed in life with such confidence. Four lesions that conformed to the echocardiographic criteria of "false aneurysms" (pseudoaneurysms) were found to be "true" aneurysms when their wall was subsequently examined histologically. The histological criteria used to establish the myocardial origin of the aneurysm wall were the presence of residual islands of myocytes and coronary arteries draping the external surface of the sac. Both criteria are established as the morphological features that distinguish true aneurysms from pseudoaneurysms, in which there is no residual myocardium or coronary arteries in the wall.^{2,6,7}

For true ventricular aneurysms therefore there is a spectrum from those with a wide neck, at one extreme, to those with a narrow neck relative to the size of the aneurysm sac at the other extreme (figure). It is aneurysms with narrow necks that cannot be distinguished from pseudoaneurysms at echocardiography. Aneurysms with narrow necks and large external sacs that extend behind the intact portion of the ventricular wall produce a typical parrot beak outline on angiography and can be identified as pseudoaneurysms with more certainty. Pseudoaneurysms with a similar shape occur as congenital diverticula or after trauma.^{9,10}

The spectrum of shapes in true ventricular aneurysms may result from the different mechanisms by which they are formed. All ischaemic ventricular aneurysms arise from transmural infarction¹¹; aneurysms can arise through the stretching, sliding, or tearing of muscle bundles in the necrotic myocardium of the acute infarct. The acute infarct rapidly stretches to form an aneurysm, and later fibrous replacement merely stabilises the existing shape. An alternative mechanism is that the aneurysm does not

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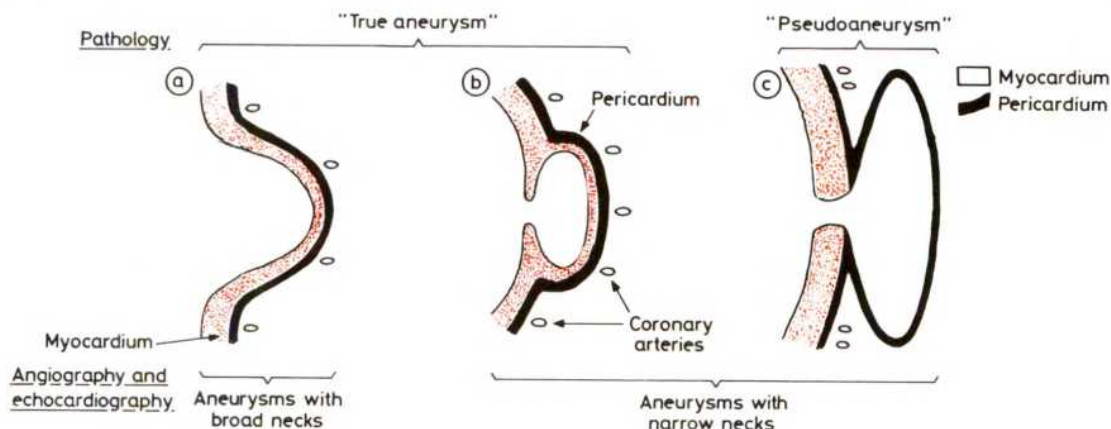


Figure Aneurysms with narrow necks on echocardiography (b, c) may either have their wall derived from the myocardium or the pericardium. So clinical use of the terms "true" and "false" is confusing and irrelevant.

begin to form until the necrotic infarct has at least, in part, been replaced by fibrous tissue, and aneurysm growth is the result of the weakness of recently formed collagen under high stress; if an aneurysm has not formed by three months the reparative fibrosis is sufficiently established to prevent any dilatation of the healed infarct.³

There is experimental evidence that stretching of necrotic myocardial tissue before the start of fibrous replacement is the predominant mechanism of aneurysm formation.¹² In human beings acute expansion is a feature of anterior infarction and is associated with a high early mortality from rupture. Once the aneurysm is stabilised by replacement of the necrotic tissue by collagen the risk of rupture becomes slight but mortality from heart failure remains high.³ Infarct expansion is rare in the acute phase of posterior/inferior infarction yet posterior aneurysms with narrow necks are twice as common on the posterior wall as on the anterior wall, which suggests that the process leading to the formation of posterior aneurysms is different. Small endocardial tears often develop over acute infarcts; such tears may allow the formation of an intramural haematoma and may provide the basis for the development of a narrow necked aneurysm with walls derived from the subpericardial myocardium. The tendency for narrow necked aneurysms to be more common on the posterior/inferior wall may also reflect variation in myocardial thickness or support by surrounding structures such as the base of the papillary muscles.

Because echocardiography cannot distinguish the exact origin of the wall in aneurysms with a narrow neck, the terms "true" and "false" have no clinical

relevance. Such a distinction can only be made by pathological examination. The risk of late rupture is said to be higher for aneurysms with narrow necks than for those with broader necks.^{4,6,13,14} If this is true, it probably reflects the thickness of the aneurysm wall rather than its histological origin (that is myocardium or pericardium). Claims that aneurysms with narrow necks are much more susceptible to late rupture are, however, largely based on necropsy reports of a few fatal cases and not on a valid estimate of the number of living subjects at risk with unruptured aneurysms of this type.

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Limitations on the prognostic value of predischage data after myocardial infarction

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SUMMARY Clinical variables and those obtained by non-invasive techniques were studied prospectively in a series of 306 patients discharged from hospital after an acute myocardial infarction. The predictive value of the data at two and 12 months was assessed by univariate and multivariate analyses. The best correlation was found for age, hypertension, bundle branch block, early and late heart failure, x ray cardiothoracic ratio, digoxin use, the number of metabolic equivalents reached during the stress test, echocardiographic wall motion score index, left ventricular end diastolic diameter, left ventricular ejection fraction, and the presence of an aneurysm. The prognostic value of the same data at 12 months was studied in those surviving for two months. There was a noticeable decline in the relative risk of all but two of the factors (number of metabolic equivalents, ventricular arrhythmias). All of the predictive variables except the x ray cardiothoracic ratio, number of metabolic equivalents, and the presence of an aneurysm lost their discriminant power. The explanation for this is the strength of statistical relations of these variables with the outcome at two months. They continued to influence the score at 12 months even when the entire patient series was considered.

In conclusion, the study shows that the predictive value of most of the predischage variables usually taken into account in the assessment of risk in patients one year after infarction does not extend beyond the first two months.

In a previous prospective study we analysed the clinical data and information obtained by all currently available non-invasive techniques in a series of 202 patients in hospital with acute myocardial infarction.¹ The relevance and predictive values of some of the resulting indices were then established for a two month follow up period. The study was extended to 306 patients with the aim of assessing the validity of our previous work, extending the survey up to one year, and focusing more attention on follow up of those who survived two months.

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Patients and methods

We studied a continuous series of men aged <70 who were admitted to the coronary care unit from January 1981 to March 1985 within 24 hours of the first clinical signs of myocardial infarction and left the hospital alive. The criteria for infarction were a peak serum concentration of creatine kinase MB that was $\geq 50\%$ of the upper normal limit and either the characteristic electrocardiographic signs of myocardial infarction or a history of prolonged chest pain consistent with this diagnosis. Three hundred and twenty two of the 905 patients admitted with myocardial infarction during this selection period met these criteria. Fifteen patients were excluded because of severe concurrent illnesses (6) or because they were foreigners who usually lived abroad (9). Of the remaining 307 patients considered for follow up, one

died from a non-cardiac illness in the first two months of follow up and another died between the second and twelfth months. So 306 patients were included in the statistical analyses of the two month follow up and 305 were included in the 12 month follow up.

During hospital admission the patients were managed in accordance with the usual clinical indications. Forty five (15%) patients were treated with streptokinase. At the time of discharge, 150 (49%) subjects were taking β blockers, 34 (11%) anti-arrhythmic drugs, and 25 (8%) digoxin.

All patients were followed up for two and 12 months, with death as the end point. Only one patient was lost to one year follow up. The predictive value of the data collected before discharge was measured at two and 12 months. The predictive value at 12 months was also measured for those who survived the first two months.

VARIABLES

During the hospital stay 68 variables were investigated as described in our previous report.¹ They included history; clinical, electrocardiographic, and laboratory data; chest x ray cardiothoracic ratio, and the results of all of the non-invasive tests that were performed—that is treadmill exercise test, M mode and cross sectional echocardiography, gated equilibrium radionuclide ventriculography, and a 24 hour ambulatory electrocardiogram. These tests were carried out between 10 and 12 days after the myocardial infarction, before the date of discharge and without stopping drug treatment.

EXERCISE TEST

The exercise test was performed on a treadmill.² The maximum exercise level was expressed in metabolic equivalents and heart work was evaluated by the double product (systolic blood pressure $\times$ heart rate). ST changes were considered to be abnormal when there was a displacement of >1 mm in three consecutive complexes with a stable baseline. ST depression was measured 0.06 s after the RST (J) junction.

ECHOCARDIOGRAPHIC ANALYSIS

Echocardiograms were recorded on an ATL Mk 300. We measured long and short diameters of the left ventricle and the shortening fraction (%). Segmental wall motion was analysed by standard methods.^{3,4} The left ventricle wall was divided into 16 segments and each segment was then assigned a number corresponding to the wall motion analysis (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, 5 = aneurysm). The sum of these numbers multiplied by 10 and then divided by the

number of segments visualised gave the wall motion score index.

GATED EQUILIBRIUM RADIONUCLIDE VENTRICULOGRAPHY

Gated equilibrium radionuclide ventriculography was performed in the left anterior oblique (40°) and left posterior oblique (30°) projections a few minutes after intravenous injection of 15 mCi of technetium-99m labelled human serum albumin. The left ventricular end systolic and end diastolic volumes were measured and the left ventricular ejection fraction was calculated. We used a temporal Fourier transform to evaluate regional wall motion from functional images.^{5,6}

TWENTY FOUR HOUR ELECTROCARDIOGRAPHIC RECORDING

A patient was considered to have ventricular arrhythmias if 200 or more extrasystoles, runs, or ventricular tachycardia (≥ 5 beats) were recorded over a 24 hour period. The patients were active and able to walk about in the ward while the electrocardiograms were being recorded.

STATISTICAL ANALYSIS

The data collected during the hospital stay were analysed for correlations with the occurrence of cardiac death two and 12 months after admission to the coronary care unit. The predictive value of all of the variables was assessed by univariate statistical analysis and stepwise discriminant analysis for both follow up periods. The relative risks for all three periods (two months, 12 months, and from two to 12 months) were also calculated. All the analyses were performed with the Statistical Package for Social Sciences (SPSS), version 8 PO.⁷⁻⁹

Results

Fourteen (4.6%) patients died within two months of admission: eight suddenly, one from a recurrent myocardial infarction, and five from heart failure. A further 22 (7%) patients died between two and 12 months: nine from sudden death, six from another myocardial infarction, and seven from heart failure.

UNIVARIATE ANALYSIS

Predictive value at two and 12 months for all patients alive at the time of discharge

Clinical data (table 1).—The mean age difference between those who survived and those who died was significant at the one year follow up only. Hypertension was also predictive of death for the 12 month period only. No significant differences were found for a history of angina, previous infarctions, or

Table 1 Predictive value (%) at two and 12 months of clinical, electrocardiographic, and radiological data determined by univariate analysis (for all patients leaving the hospital alive)

Variables	2 months			12 months		
	Alive (n = 292)	Dead (n = 14)	p	Alive (n = 269)	Dead (n = 36)	p
Age (mean (SD))	56.0 (8.3)	58.8 (8.3)	NS	55.8 (8.4)	59.1 (6.6)	<0.05
Hypertension	26	43	NS	25	44	<0.05
Angina	33	50	NS	33	36	NS
Previous MI	26	50	NS	26	33	NS
Diabetes	25	36	NS	26	28	NS
Anterior MI	43	50	NS	42	52	NS
VT, VF	23	36	NS	24	22	NS
Bundle branch block	8	29	<0.05	8	19	<0.05
Early heart failure	17	86	<0.001	16	53	<0.001
Late heart failure	5	21	<0.05	4	17	<0.01
x ray C.T. ≥ 50	39	86	<0.01	37	81	<0.001
Digoxin	7	36	<0.001	6	22	<0.01
β Blocking agent	50	36	NS	50	47	NS

MI, myocardial infarction; VT, ventricular tachycardia; VF, ventricular fibrillation; C.T, cardiothoracic ratio.

diabetes. Neither the infarction site nor the presence of ventricular tachycardia or fibrillation during hospital stay had any significant predictive value. The peak increase in plasma creatine kinase MB was lower in survivors at both two months (mean (SD) 50 (33) v 91.3 (98) $\mu\text{g/ml}$) and 12 months (mean 49 (91) v 71 (69) $\mu\text{g/ml}$). Nevertheless, the F test showed a highly significant difference in the variances in both groups. So a *t* test with "separate variance estimate" was chosen. This showed no significant difference between the mean plasma concentrations of creatine kinase MB. Complete right or left bundle branch block were less frequent at both two and 12 months in those who survived than in those who died. The variables related to deterioration of left ventricle function had especially high predictive values of death. Early heart failure (Killip classes II and III in the first three days after the acute myocardial infarction) was noted in 17% of the survivors and 86% of those who had died by two months and 16 and 53% of the survivors and those who had died by 12 months. Heart failure at the time of discharge (late heart failure) also showed a predictive value at two months

(5% v 21%) and 12 months (4% v 17%). A cardiothoracic ratio $\geq 50\%$ and digoxin use were also predictive of death, before two and 12 months. Neither β blocking agents, nor antiarrhythmic treatment, nor angina at the time of discharge had discriminant value at two and 12 months. Streptokinase did not have any significant impact on prognosis, but only 45 patients received this drug.

Non-invasive procedures—The exercise test (table 2) was undertaken by 295 patients. The one year mortality for this group was 11.5%, compared with 18% for the patients who were unable to perform the test because of heart related (arrhythmias, heart failure) or other reasons. Of the variables that were indicative of exercise capacity, only the mean peak workload, expressed in metabolic equivalents, achieved by the patients was higher in the survivors at two and 12 months. ST depression or elevation was not of predictive value. Even severe ST depression or elevation (> 2 mm) failed to have predictive value.

Several echocardiographic findings were of interest (table 3). The mean value of the wall motion

Table 2 Predictive value at two and 12 months after myocardial infarction of predischARGE exercise testing for surviving and dead patients determined by univariate analysis (for all patients leaving the hospital alive)

Variables	2 months			12 months		
	Alive (n = 282)	Dead (n = 13)	p	Alive (n = 261)	Dead (n = 33)	p
METs (mean (SD))	3.7 (1.7)	2.5 (1.5)	<0.01	3.8 (1.6)	2.4 (1.5)	<0.001
Max heart rate (mean (SD))	102 (15)	105 (15)	NS	102 (15)	102 (17)	NS
Double product (mean (SD))	14.2 (4)	12.8 (4)	NS	14.2 (4)	13.1 (4)	NS
ST depression > 1 mm (%)	42	25	NS	43	30	NS
ST elevation > 1 mm (%)	36	40	NS	35	36	NS
Severe ST depression or elevation (> 2 mm) (%)	24	17	NS	23	25	NS

METs, metabolic equivalents.

Table 3 Predictive value at two and 12 months of echocardiographic data for surviving and dead patients determined by univariate analysis (for all patients leaving the hospital alive)

Variables	2 months			12 months		
	Alive (n = 254)	Dead (n = 13)	p	Alive (n = 234)	Dead (n = 32)	p
WMSI (mean (SD))	15.9 (5.3)	22.5 (4.8)	<0.001	15.8 (5.3)	19.5 (5.7)	<0.001
WMSI > 22 (%)	13.4	76.9	<0.001	12.8	43.5	<0.001
LVEDD (mean (SD))	57.0 (6.9)	65.5 (5.7)	<0.001	57.0 (6.9)	60.8 (8.9)	<0.01
Aneurysm (%)	12	31	NS	11	28	<0.01

WMSI, wall motion score index; LVEDD, left ventricular end diastolic diameter.

score index and scores above 22 had discriminant value at two and 12 months. At two and 12 months the mean left ventricular end diastolic diameter was greater in those who died. Left ventricular aneurysms were statistically less frequent in those who were still alive at 12 months. Radionuclide ventriculography (table 4) showed higher mean left ventricular ejection fractions in survivors at two and 12 months. Left ventricular aneurysms were less frequent in survivors at two and 12 months. Ventricular arrhythmias (as defined above) were less common in the 24 hour electrocardiograms of survivors but the difference was significant at 12 months only.

Predictive values of the same variables at one year for those who survived the first two months (291 cases)

In order to establish their predictive value at 12 months the predischARGE data were re-examined for the group that survived the first two months. The non-predictive data for all patients remained non-predictive for this group.

Table 5 summarises the data with significant prognostic value for all patients (at two or 12 months or both). At 12 months only four of these variables continued to have a significant relation to the outcome in those who survived the first two months. These were a cardiothoracic ratio $\geq 50\%$, the functional capacity during the exercise test, isotopically detected left ventricular aneurysms, and ventricular arrhythmias in the 24 hour electrocardiographic recordings. The other variables lost their predictive, discriminant value.

Table 5 Predictive value (%) at 12 months of clinical and technical variables determined by univariate analysis (for the patients surviving for the first two months)

Variables	Alive	Dead	p
Age (mean (SD))	55 (8.4)	59 (7.2)	NS
Hypertension	25	46	NS
Early heart failure	16	32	NS
Bundle branch block	8	14	NS
Late heart failure	4	14	NS
x ray C:T $\geq 50\%$	37	77	<0.001
Digoxin	6	14	NS
METs (mean (SD))	3.8 (1.6)	2.3 (1.5)	<0.001
WMSI (mean (SD))*	15.8 (5.3)	17.4 (5.6)	NS
LVEDD diameter (mean (SD))*	57 (6.9)	55.5 (7.8)	NS
Aneurysm*	11	26	NS
LVEF $\leq 40\% \dagger$	24	45	NS
Aneurysm $\dagger$	17	55	<0.01
Ventricular arrhythmias $\ddagger$	26	50	<0.05

C:T, cardiothoracic ratio; METs, metabolic equivalents; WMSI, wall motion score index; LVEDD, left ventricular end diastolic diameter.

*Echocardiographic data. $\dagger$ Radionuclide data. $\ddagger$ 24 hour electrocardiogram

Relative risk of death

The relative risk of death for a given variable is the ratio of the mortality observed for the group with this factor to the mortality observed for the group without this factor. It was calculated for all variables showing a statistically significant predictive value for at least one of the periods investigated—that is two months, 12 months, and from two to 12 months (table 6).

Comparison of the relative risks of death for the three periods showed large intravariation differences between the periods and intervariable differences for

Table 4 Predictive value at two and 12 months of radionuclide ventriculography for surviving and dead patients determined by univariate analysis (for all patients leaving the hospital alive)

Variables	2 months			12 months		
	Alive (n = 263)	Dead (n = 12)	p	Alive (n = 242)	Dead (n = 32)	p
LVEF (mean (SD))	48 (14)	30 (13)	<0.001	49 (13)	38 (15)	<0.001
LVEF $\leq 40\%$	25	75	<0.001	24	56	<0.001
Aneurysm (%)	19	50	<0.05	17	47	<0.001

LVEF, left ventricular ejection fraction.

Table 6 Relative risk calculated at two and 12 months (for the entire population and for patients surviving for the first two months)

Variables	2 months	0-12 months	2-12 months
Hypertension	2	2.1	2.3
Early heart failure	23.8*	4.2*	2.2
Bundle branch block	4*	2.4*	1.8
x ray C.T. $\geq 50\%$	8.5*	5.7*	5.1*
Late heart failure	4.4*	3.2*	2.9
Digoxin	6.2*	3.2*	3.1
METs < 3	2.4*	4.0*	6.4*
WMSI > 22 †	17.5*	3.8*	1.7
Aneurysm†	3	2.6*	2.6
LVEF $< 40\%$ ‡	7.9*	3.3*	2.4
Aneurysm‡	3.8	3.4*	3.4*
Ventricular arrhythmias§	1.7	2.2	2.6*

C.T., cardiothoracic ratio; METs, metabolic equivalents; WMSI, wall motion score index; LVEF, left ventricular ejection fraction.

*Predictors of mortality that were statistically significant by univariate analysis. †Echocardiographic data. ‡Radionuclide data. §24 h electrocardiogram.

the same period. At two months, the highest risks were associated with early heart failure (23.8) and an x ray cardiothoracic ratio of $\geq 50\%$ (8.5) (for the clinical factors) and a wall motion score index above 22 (17.5) and an isotopically determined left ventricular ejection fraction $\leq 40\%$ (17.9) (for the non-clinical variables). For all but two factors the relative risk at 12 months for all patients was lower than the relative risk at two months. For metabolic equivalents and arrhythmias the relative risk rose (from 2.4 to 4 and from 1.7 to 2.2 respectively). The decrease in risk was especially pronounced for the two factors that had the highest scores at two months, namely, early heart failure (decreasing from 23.8 to 4.2) and a wall motion score index above 22 (falling from 17.5 to 3.8). When the risks at 12 months for all of the patients included in the study were compared with those who survived the first two months there was a further decrease in the relative risk for most of the variables. The relative risk remained almost unchanged for the presence of an aneurysm but increased for the metabolic equivalents and ventricular arrhythmias.

Table 7 Independent predictors of death determined by multivariate analysis at two and 12 months follow up (for all patients and for the group surviving the first two months)

Variables	Standardised coefficient at:		
	2 months	12 months	2-12 months
Early heart failure	0.74***	0.35***	—
x ray C.T. $\geq 50\%$	0.41**	0.57***	0.61**
METs	—	-0.46***	-0.57***
Aneurysm (radionuclide)	—	—	0.31*

C.T., cardiothoracic ratio; METs, metabolic equivalents.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

MULTIVARIATE ANALYSIS

Stepwise discriminant analysis was performed at two months; it was repeated at 12 months for the entire sample group and for those who survived the first two months.

The following variables were introduced in the discriminant function in the first step: early heart failure, x ray cardiothoracic ratio, number of metabolic equivalents reached during the stress test, radioisotopically determined left ventricular ejection fraction, bundle branch block, wall motion score index, and ventricular arrhythmias. Except for heart failure, these variables were weakly correlated (maximum 0.30).

The following independent predictors of death, listed by order of entry, emerged: at two months—early heart failure (standardised coefficient 0.74, $p < 0.001$) and x ray cardiothoracic ratio $\geq 50\%$ (0.35, $p < 0.01$); at 12 months—early heart failure (0.35, $p < 0.001$), x ray cardiothoracic ratio $\geq 50\%$ (0.57, $p < 0.001$), and the number of metabolic equivalents during the stress test (-0.46, $p < 0.001$). When the 12 month follow up was limited to those who survived the first two months, early heart failure disappeared as an independent predictive factor. Two variables remained significant. These were, by order of entry, x ray cardiothoracic ratio $\geq 50\%$ (0.61, $p < 0.01$) and the number of metabolic equivalents (-0.57, $p < 0.001$), while a ventricular aneurysm detected by the radionuclide method was an independent predictive factor (0.31, $p < 0.05$). Heart failure, which was highly correlated with the other factors, was excluded in the second step. The same variables remained significant (table 7).

Discussion

A previous study of 202 patients emphasised the predictive value of simple clinical and non-invasive factors at two months.¹ The present study, including the first 202 patients and extended to 306 patients, and in which all factors retained their earlier significance, confirmed the results of the first study.

The 12 month extended follow up, with only one patient lost to follow up, showed that the same factors continued to be of prognostic value, especially those that were indicative of impaired left ventricular function—that is early heart failure, an enlarged heart by radiography, a score < 3 metabolic equivalents during exercise testing, the echocardiographically determined wall motion score index, left ventricular ejection fraction, and the presence of an aneurysm (radionuclide method). A history of hypertension became significant. Nevertheless, the relative risk of death for all but two of the factors was lower at 12 months than at two months.

We did not find any relation between ST change and mortality, contrary to other investigators' reports.¹⁰⁻¹² Surprisingly, ST changes > 1 mm were more frequent among the survivors. Methodological differences, lower exercise levels (for the patients' safety, testing was stopped if relatively mild subjective and objective signs developed, as confirmed by the low maximum heart rate), and the administration of β blockers and digoxin may account, at least partially, for these differences. Nevertheless, the exercise test was carried out between days 10 and 12 in 96% of our subjects and was thus representative of the entire sample. Furthermore, others have reported the lack of correlation between ST segment changes and survival¹³⁻¹⁵ and bypass surgery performed in some of the patients during the first year of follow up may reduce the predictive value of ST depression.¹²⁻¹⁵ Fifty two of our patients had coronary artery bypass grafts between two and 12 months; the decision to operate was prompted by the results of the exercise test. Of this group, 61% showed significant ST depression during exercise. The 24 hour electrocardiographic monitoring was done rather early (between days 10 and 12), which may also account for the lack of prognostic value at two months.¹

When the 12 month follow up was limited to the two month survivors, most of the predictive factors were no longer discriminant (only four out of the 14 were still useful), while the relative risk of death associated with most of the factors declined.

The different statistical methods used (univariate and stepwise discriminant analysis) and relative risk calculations gave similar information. Specifically, the changes in the values of the different factors studied for the three follow up periods followed similar patterns.

The prognostic factors and indices were generally evaluated at 12 months after the acute event. While the results of our 12 month follow up were consistent with current knowledge for most of the variables, the study showed that the one year significance of most of the prognostic factors was influenced by the strength of their ability to predict death at two months. When the very ill patients who died within the two month follow up period were excluded, the findings for the remaining subjects for the two to 12 month follow up period were quite different. This explains why most prognostic variables lost their statistical significance. It is clear that the short term prognosis correlated strongly with the variables related to the size of the infarcted area and the degree of left ventricular dysfunction. After the two month period the long term prognosis is probably most dependent on other factors, such as the course of coronary disease. Further investigations at the end of the second month would probably improve the accuracy of the one year prognosis.

In conclusion, our findings show that the predictive value of most of the predischARGE clinical and technical data gathered on acute myocardial patients and used in establishing the 12 month prognosis is only valid in the short term. For two month survivors, more useful information could perhaps be gleaned from data obtained at that time.

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Risk factors for embolisation in patients with left ventricular thrombi and acute myocardial infarction

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SUMMARY Risk factors for systemic embolisation in patients with ventricular thrombi caused by an acute myocardial infarction were studied in 150 consecutive patients with an infarction of the anterior wall. Serial echocardiograms were performed 2-10 days after the acute event and patients were followed up for three months. Anticoagulation treatment was started only after the detection of thrombi. Of the 55 patients in whom a thrombus developed, 15 (27%) had peripheral emboli between 6-62 days; but only two (2%) of 95 patients without thrombus had emboli. Among 15 variables, the best single predictors of embolisation were age > 68 years (80% sensitive, 85% specific), pendulous thrombus (60%, 93%), and independent thrombus mobility (60%, 85%). Logistic regression analysis showed that a formula that included patient age, thrombus area, and the length of thrombus in the ventricular lumen predicted embolisation (sensitivity 87%, specificity 88%). There was no correlation between age and the thrombus variables.

The risk of embolisation from left ventricular thrombi in acute anterior myocardial infarction can be accurately assessed from patient age and echocardiographic features. The risk of peripheral emboli is high in patients with left ventricular thrombi and those aged > 68.

Left ventricular thrombi were detected by cross sectional echocardiography in 28-40% of patients with anterior wall acute myocardial infarction but rarely occurred with infarcts at other sites.¹⁻⁸ The reported risk of embolisation after the formation of a thrombus ranges from 0 to 37%.¹⁻¹³ Several of these reported studies were retrospective or small.

Several predictors of embolisation have been defined in patients who have left ventricular thrombi. In particular, mobile and pendulous thrombi have been associated with an increased frequency of embolisation. But the frequency of embolisation in patients with thrombus protrusion into the left ventricle (22%-100%) or thrombus mobility (35%-100%) has varied widely.⁹⁻¹⁴ These wide differences may be associated with differences in patient populations (recent versus remote infarctions), differences in anticoagulant treatment, or with the fact that some of the studies were retrospective.⁹⁻¹¹ Several studies found that thrombi with very different echocar-

diographic appearances were associated with embolisation.¹⁴⁻¹⁶ Moreover, one recent study of acute thrombi noted considerable spontaneous variability of both thrombus mobility and shape, which makes these features less useful predictors for embolisation.¹² So, further data are needed on predictors of embolisation.

The objectives of the present prospective study were to define the risk of embolism associated with left ventricular thrombi in patients with a first acute anterior infarction and to identify predictors of embolisation.

Patients and methods

One hundred and fifty consecutive patients with an initial acute anterior wall myocardial infarction were examined prospectively by cross sectional echocardiography for the development of left ventricular thrombi. The criteria for acute myocardial infarction were (in addition to a typical history): (a) the development of Q waves and/or ST-elevation of ≥ 1 mm in standard leads I and aVL and/or ≥ 2 mm in precordial leads V1-6 followed by T wave inversion and (b) a transient increase in aspartate aminotransferase to more than twice the upper limit of normal.

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Patients taking anticoagulants or platelet inhibiting drugs were excluded from the study.

None of the patients received any type of anticoagulation before the diagnosis of a left ventricular thrombus. Only patients who developed a definite left ventricular thrombus were given intravenous heparin (therapeutic level for partial thrombin time 70–140 seconds)¹⁷ and oral warfarin (therapeutic Thrombotest level 5–10%).¹⁸ Heparin was stopped when the Thrombotest became normal, but warfarin was continued throughout the study period. Patients who did not develop a thrombus were not given anticoagulants, and anticoagulants were not started in 15 patients who had contraindications to anticoagulants. Platelet inhibiting drugs and prophylactic antiarrhythmic drugs were not used.

CROSS SECTIONAL ECHOCARDIOGRAPHY

Between days 2 and 10 after the acute infarction serial cross sectional echocardiographic examinations were performed with a Toshiba SSH-10 phased array sector scanner. All patients had at least three examinations; if no thrombus was diagnosed, patients were generally examined on day 2, 6, and 10. Once a thrombus was suspected, more frequent examinations were performed and if necessary continued after day 10 to make a definite diagnosis. Patients who did not have a left ventricular thrombus present within 10 days were not examined further, while patients in whom a thrombus had been detected had monthly echocardiograms.

Patients were examined while they were lying in the left lateral decubitus position with the head slightly raised. Our diagnostic criteria for thrombi were: (a) intracavitary mass visible with two markedly different sector orientations; (b) an intracavitary mass with a definite margin; and (c) clear delineation of the underlying endocardium. Studies were interpreted by two independent observers. There was disagreement on six patients, but a consensus was reached by both observers when they reviewed the serial scans. Patients were not excluded because of poor image quality; one observer considered the images to be of poor quality in 11 patients and the other observer considered image quality to be poor in nine of the same patients. None of the patients who had poor image quality were diagnosed as having a thrombus.

CHARACTERISATION OF THROMBI

Thrombi were characterised both visually and quantitatively.

(a) Visual features

Thrombi were classified as pendulous or flat and as mobile or immobile. Mobility was diagnosed if a

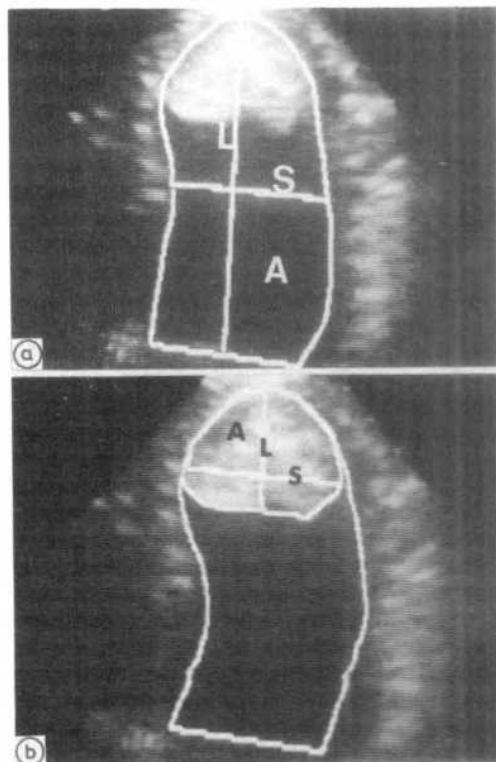


Fig 1 Area A of the manually drawn outline of the left ventricle (a) and left ventricular thrombus (b) with the long axis (L) and short axis (S).

thrombus or parts of it showed movement that differed from that of the underlying myocardium during the cardiac cycle. In addition, a thrombus was classified as either homogeneous or heterogeneous. A thrombus was classified as heterogeneous if parts of it had a shaggy margin or if its centre was echolucent.

(b) Quantitative features

We used a light pen and overlay technique,¹⁹ to calculate the area, long axis, and short axis of both the ventricle and the thrombus (fig 1 a–b). The area under the manually drawn ventricular end diastolic (peak of R wave in standard electrocardiographic lead I) silhouette was computed in the apical four chamber view with the transducer position that gave the largest ventricular area. We measured the long axis from the middle of the mitral valve to the apex in the same view and the short axis as the transverse diameter in the same four chamber view at the middle of the long axis (fig 1a).

We measured the thrombus on the view in which it was largest and had a definite margin. We avoided transducer positions that might have included myocardium as well as thrombus. Although ven-

Table 1 Characteristics of patients with left ventricular thrombi (LVT) and peripheral emboli (PE)

	Patients with LVT and PE (n = 15)	Patients with LVT and no PE (n = 40)	p
Age (yr)	68.9 (6.0) (55-79)	59.1 (8.1) (35-76)	<0.001
Peak ASAT (U/l)	359 (224) (119-820)	333 (146) (83-699)	NS
Time from infarction to diagnosis of thrombus (days)	7.2 (3.4) (3-16)	6.5 (3.9) (2-23)	NS
Number of patients with Q wave infarctions	11 (73%)	31 (78%)	NS

ASAT, aspartate aminotransferase. Results are mean (SD) (range).

tricular thrombi are more echo dense than the blood and the endocardium and myocardium, we could not always identify the border between the endocardium and the thrombus. In such cases, the thrombus border was drawn as a smoothed curve along the endocardial border where the echo density became considerably less than that of the thrombus border against the ventricular lumen. We outlined the area of the thrombus and measured the length from the apical endocardium to the intraventricular border (thrombus long axis, L) and the orthogonal width (thrombus short axis, S) (fig 1b).

Thrombi were measured when there was a definite diagnosis of a left ventricular thrombus. This did not necessarily coincide with the first day the thrombus was suspected. Subsequent changes in the appearance of the thrombus were used to change only the visual variables in the thrombus classification.

Two observers did all the measurements. The interobserver variability in the quantitative analysis of the 55 thrombi was $< \pm 15.5\%$ for areas, $< \pm 8\%$ for long axis, and $< \pm 14.7\%$ for transverse axis measurements. The intraobserver variability was less than this.

PERIPHERAL EMBOLI

All patients were followed for three months for the occurrence of peripheral emboli. Patients were told to report immediately if symptoms of peripheral embolisation developed.

Peripheral embolisation was defined as: (a) acute arterial occlusion in an extremity or (b) acute cerebrovascular accident with neurological symp-

toms and findings that persisted for at least one hour. Dizziness, syncope, or symptoms with no abnormal clinical neurological findings were not accepted. We did not attempt to diagnose emboli in the abdominal circulation. Computerised cerebral tomography was done on eight of the 12 patients with thrombus and stroke and in two patients with stroke but no thrombus. All patients with a diagnosis of emboli were examined on the day of the embolic event.

STATISTICAL ANALYSIS

We used Fisher's exact test to analyse discontinuous data and stepwise logistic regression to compare the data from patients with and without peripheral emboli.²⁰ Mean values of the variables from the two groups were compared by the Wilcoxon-Mann Whitney test, and correlations between normally distributed continuous variables were analysed by linear regression. All tests were two sided, and p values of < 0.05 were regarded as significant. Results are given as mean (1 SD).

Results

Of the 150 patients, 55 (37%) developed a left ventricular thrombus and 95 (63%) did not. Among the 95 patients without a diagnosis of thrombi, only two (2%) suffered cerebrovascular accidents (8 and 14 days) after the infarction. Fifteen (27%) of the 55 patients with thrombi had peripheral emboli from five to 62 days after the acute infarction. Ten (67%) of the 15 embolic events occurred during the first

Table 2 Computerised measures of the left ventricle and left ventricular thrombi

	Thrombus and PE	Thrombus, no PE	p
Left ventricle:			
Area (cm ²)	40.7 (7.1) (28.7-51.2)	40.2 (6.5) (28-58)	NS
Long axis (cm)	9.6 (1.1) (7.9-11.4)	9.0 (0.7) (7.6-10.5)	<0.025
Transverse axis (cm)	4.8 (0.7) (3.7-6.3)	5.1 (0.9) (3.6-8.1)	NS
Thrombus:			
Area (cm ²)	5.1 (2.0) (1.7-10.0)	5.3 (3.4) (1.8-19.4)	NS
Long axis (cm)	2.4 (0.6) (1.3-3.2)	1.7 (0.5) (1.2-3.6)	<0.001
Transverse axis (cm)	2.9 (0.9) (0.8-4.3)	3.3 (1.2) (1.2-6.9)	NS
Thrombus area/ventricle area ratio	0.13 (0.08) (0.04-0.47)	0.13 (0.05) (0.06-0.25)	NS

PE, peripheral emboli. Results are mean (SD) (range).

Table 3 Predictive value of patient age and visual variables of left ventricular thrombi (LVT) for peripheral emboli (PE)

	Patients with LVT and PE (n = 15)	Patients with LVT and no PE (n = 40)	Sensitivity (%)	Specificity (%)
Patient age > 68 years	12	6	80	85
Independent movement	9	6	60	85
Pendulous form	9	3	60	92.5
Variable echo density	10	7	66.7	82.5

three weeks after the acute infarction, and 12 (80%) were cerebrovascular accidents. The mean age of the 55 patients with left ventricular thrombus was 61.8 (8.2) years compared with 61.5 (10.0) years (NS) in the 95 patients without a thrombus.

Table 1 compares thrombus patients with and without emboli. The mean values of peak aspartate aminotransferase activity, time from onset of the infarction to diagnosis of thrombus, and the occurrence of Q wave infarctions or transient arrhythmias during the first 10 days were not different in the 15 patients with (group 1) and the 40 patients without (group 2) peripheral emboli. Patients with peripheral emboli were significantly older than those without (68.9 (6.0) versus 59.1 (8.1), $p < 0.001$).

The long axis of the left ventricle was slightly longer in patients with emboli than in those without (table 2). In addition, the long axis of the thrombus was significantly greater in patients with emboli (2.4 (0.6) cm versus 1.7 (0.5) cm, $p < 0.001$). Other measurements of the ventricle or thrombus were not significantly different in groups 1 and 2. Only one of the 10 largest thrombi, as judged by thrombus area, formed emboli.

The predictive value of the following variables was analysed: patient age, sex, time from start of symptoms to admission, time from infarction to thrombus development, peak aspartate aminotransferase, left ventricular area, long and transverse axis, thrombus area, long and transverse axis, relation between thrombus area and ventricular area, independent movement of thrombus, echolucency of thrombus, and pendulousness of the thrombus.

Age was the best single predictor of peripheral embolus. Of the 55 patients with thrombus, 12 of 15 who had embolisation were > 68 (sensitivity = 80%) whereas only six patients without embolisation were > 68 (specificity = 85%) (table 3). Thus 12 (68%) of the 18 patients with thrombus who were aged > 68 had emboli, whereas only two (9%) of 22 patients > 68 years without thrombi had a cerebrovascular accident ($p < 0.001$).

The single best visual predictor of embolisation was pendulousness. Pendulous thrombi were present in nine of 15 patients with emboli compared with three of 40 patients without (sensitivity 60%, specificity 93%). The thrombus was mobile in nine

of 15 patients with emboli and six of 40 without emboli (sensitivity 60%, specificity 85%). Of the 17 thrombi with variable echo density, 10 had central echolucency and seven had varying echo density without a central clearing.

The following predictive equation for peripheral embolisation that includes patient age (Y), the thrombus area (A), and the long axis of the thrombus (L) was established by a stepwise logistic regression: (1) Probability of embolus = $1/(1 + \exp(1.05 \times A + 25.2 - 0.284 \times Y - 5.67 \times L))$.

Figure 2 shows the calculated probabilities of embolisation in the patients with thrombi. We chose some arbitrary cut off points for the probability of emboli and calculated the corresponding sensitivity and specificity. A cut off of 0.35 gave the highest sensitivity and specificity of 85.6% and 87.5%, respectively (fig 2). Although retrospective choice of a cut off point may be sample specific, choosing other cut offs also resulted in good predictability, higher cut offs reduced sensitivity but increased specificity.

Although there was a significant correlation between thrombus area and length ($r = 0.85$, $p < 0.001$), there was no correlation between the patient age and thrombus area or length ($r = 0.001$ and 0.09 respectively). None of the visual echocardiographic variables, however, gave additional predictive value to the logistic regression in (1).

Two of 15 patients with a left ventricular thrombus

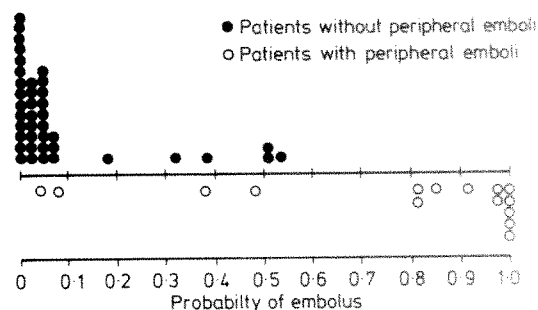


Fig 2 Distribution of the patients with left ventricular thrombi according to their calculated probabilities of peripheral emboli based on the formula: Probability of embolus = $1/(1 + \exp(1.05 \times A + 25.2 - 0.284 \times Y - 5.67 \times L))$ (Y = patient age).

Table 4 Patients with acute vascular accidents (VA)

Patient No	Time (days) from infarction to diagnosis of:		Duration (days) of anticoagulation at time of VA	Location of VA
	LVT	VA		
1	4	6	2	CVA
2	5	18	13	CVA
3	5	6	1	CVA
4	8	14	6	Left arm
5	3	12	9	CVA
6	4	62	58	CVA
7	7	23	16	Right arm
8	8	36	28	CVA
9	7	16	8	CVA
10	5	15	9	CVA
11	16	22	6	Left leg
12	8	14	6	CVA
13	14	32	18	CVA
14	6	6	0	CVA
15	6	7	0	CVA
Mean (SD)	7.1 (3.6)	19.2 (14.9)	12.0 (14.8)	

CVA, cerebral vascular accident, LVT, left ventricular thrombus.

who did not receive anticoagulants had a cerebrovascular accident, whereas 13 of the 40 patients with thrombus who received warfarin had peripheral emboli ($p = \text{NS}$). All but one of the patients on warfarin had a Thrombotest of $<10\%$ at the time of embolisation. Table 4 lists the time from the onset of the acute infarction to the diagnosis of a thrombus and peripheral emboli, the location of peripheral emboli, and the time of anticoagulation treatment before the formation of peripheral emboli. No bleeding episodes were diagnosed.

None of the 15 patients with a left ventricular thrombus and peripheral embolisation had a previous history or clinical signs of peripheral arterial or carotid artery disease, cardiac valve disease, or other conditions predisposing to emboli. Among the patients who were under observation in the hospital at the time of the embolic event, none had hypotension or atrial fibrillation.

Computerised cerebral tomography was performed in 10 of the 14 patients with acute neurological deficits. All 10 had abnormal scans showing multiple infarctions in seven patients and a large single infarction in three patients.

Discussion

The current study defines several features that predict a high risk of peripheral embolisation in patients with an acute anterior infarction and a left ventricular thrombus. Old age, a pendulous thrombus, and a mobile thrombus were associated with high embolic rates. The sensitivity and specificity of the mathematical logistic regression equation that combined echocardiographic measurements and patient age were sufficiently high to be clinically

useful.

Single plane measurements of the thrombi and ventricles may not show the true volume of these three dimensional structures. But biplane imaging is often complicated by poor image quality in the apical two chamber view. Use of volumes calculated from the area and long axis of the ventricle would only introduce a derived variable that does not increase the amount of information collected from the primary data.

The equation indicates that for a given thrombus area the risk of embolisation increases with the degree to which the thrombus projects into the ventricular lumen. The risk of embolisation is higher with slender pendulous thrombi than with broad, mural thrombi. These variables were measured from the silhouette of the thrombi at the examination when the thrombus was first definitely diagnosed. Later changes in thrombus features, such as the development of central echolucency or independent thrombus motion, did not affect the embolic risk calculated from this equation. Therefore, the equation, based on the appearance of the thrombus at the time of diagnosis, may be a better predictor of risk than the visual variables, which depend upon time-consuming serial observations of the thrombi and may show changes with time that may reduce their predictive value.¹²

An earlier retrospective study found that large thrombi increased the risk of peripheral emboli.¹⁰ However, in the present study, thrombus size, as estimated from thrombus area, was not significantly larger in patients with emboli than in those without. In addition, only one of the 10 larger thrombi was associated with embolisation, suggesting that thrombus size alone does not predict the risk of peripheral emboli.

The long axis of the ventricle in the patients with thrombi and emboli was slightly larger than that in patients with thrombi and no emboli. We do not know whether a longer axis affects the apical haemodynamics in patients with an apical thrombus and thereby influences the embolic tendency.

Age >68 years, which did not correlate with the other variables in the equation, identified 80% of the patients with peripheral emboli with a specificity of 85%. Thus in patients aged >68 , the mere presence of a thrombus seems to predict peripheral emboli as accurately as detailed measurements. In those aged <68 , embolisation was uncommon, but additional thrombus variables increased the accuracy of prediction of peripheral emboli. The cause of the apparent increase in embolic risk with age is uncertain. An earlier study found no significant age difference between patients with thrombi who had emboli and those who did not.¹³

It is difficult to diagnose a cerebral event as embolic on the basis of clinical symptoms alone. Some embolic events were not diagnosed, either because they were silent or because they caused mild transient symptoms. Many emboli to the abdominal circulation are not diagnosed during life because they do not cause symptoms. Thus we have probably underestimated the incidence of embolisation.

Most of the peripheral emboli (80%) were strokes, and it is possible that some were caused by conditions other than embolisation, such as local thrombosis. In addition, elderly patients with coronary artery disease are at an increased risk of cerebrovascular atherosclerosis. None the less, none of the 15 patients with thrombus and embolisation had evidence of carotid artery disease. Moreover, seven of 10 patients who were examined by cerebral tomography had multiple cerebral infarctions, which indicates an increased likelihood of an embolic aetiology. The low frequency (2%) of cerebrovascular accidents in the 95 patients without thrombi, who were otherwise clinically similar to the patients with thrombi, also underscores the high likelihood that most of the cerebrovascular events were embolic.

The inclusion of consecutive patients avoids selection bias. We included 11 with poor quality images, but none of them were classified as having thrombi and it is possible that thrombi were missed in some of these patients. However, no embolic events occurred in this group. Overall, only two of 95 patients in whom a thrombus was not detected had a cerebrovascular accident. Even if these events were caused by emboli from the left ventricle, underdiagnosis of thrombi by echo seems to be limited.

Overall, we saw a thirteen-fold higher embolic rate in the thrombus group than in the patients without a clot. The embolic rate of 27% in patients with left ventricular thrombi accords with earlier reports, although the range is wide, from 0–35%¹⁻¹³ to 38–85%, in patients not receiving any anticoagulants.^{6,7} Use of anticoagulants varied considerably in the previous studies and several were retrospective.

Our study was not designed to compare the effect of anticoagulants with that of no treatment on the rate of peripheral embolisation; however, it showed that there were emboli in as many as 32% of the patients with thrombi when heparin and warfarin were started after a thrombus had developed. This may suggest that all patients with anterior myocardial infarction should have prophylactic anticoagulation. Other reports seem to support this conclusion.^{2,6,21-24}

In summary, a detailed study of the cross sectional echocardiographic appearance of left ventricular thrombi after acute anterior myocardial infarction can accurately predict the risk of embolisation. In addition to echocardiographic features, advanced age

is an independent risk factor.

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Long term clinical outcome of coronary surgery and assessment of the benefit obtained with postoperative aspirin and dipyridamole

A H GERSHLICK, J P LYONS, J E C WRIGHT, M F STURRIDGE, C A LAYTON, R BALCON

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SUMMARY Three hundred and twenty patients originally entered into a randomised study to assess the effect of aspirin and dipyridamole on the patency of coronary bypass grafts one year after operation were clinically reassessed a mean of 6.6 years (range 4.3-8.6) after operation. Patients were recruited between 1978 and 1982 after the present policy of total revascularisation had been adopted. During the follow up period there were 25 deaths of which 17 were due to cardiac causes (average annual cardiac mortality 0.8%). Of 280 patients available for contact, 250 (89.3%) attended an outpatient interview. Ninety four (37.6%) patients complained of recurrent angina but in only 23 (9.2%) was this severe. Two hundred and eleven (84.4%) of the 250 patients underwent exercise stress testing. There were 73 (34.6%) abnormal tests of which 52 were in the group of 94 patients with recurrent angina. Myocardial infarction occurred in nine of the 250 patients during the follow up period. Twenty six patients (10.4%) had reinvestigation for symptoms. This group had a graft occlusion rate of 52%. Half these patients have required reoperation and 20 of 22 occluded or severely stenosed grafts were replaced. In only two instances were vein grafts inserted into vessels with new disease. Half of the original group were given aspirin (330 mg three times a day) plus dipyridamole (75 mg three times a day). Of the 250 patients interviewed, 122 took aspirin and dipyridamole from the second postoperative day for a mean of 25 months, with warfarin for three months. The other 128 patients took placebo for a mean of 23 months together with warfarin for three months. This long term treatment with aspirin plus dipyridamole conferred no significant benefit for all clinical outcomes measured at a mean of 6.6 years.

Coronary artery surgery is routinely performed as a treatment for ischaemic heart disease. As well as relieving symptoms the operation has also been shown to improve survival in certain patients.¹⁻³ These trials, undertaken in the 1970s, have also helped to determine the change in graft patency rates with time. We report a further series of patients undergoing coronary artery bypass grafting after the introduction of a policy of total revascularisation.

We studied 320 patients who entered a trial between 1978 and 1982 at the London Chest Hospital. The trial was designed to assess the effect of aspirin and dipyridamole on vein graft patency at one

year. One hundred and sixty patients were randomised to receive aspirin (330 mg) and dipyridamole (75 mg) three times a day and 160 to placebo. Both groups took warfarin for the first three months after operation.⁴

We reassessed the longer term outcome of this group of patients entered into a previously reported study of vein graft patency at one year, and we evaluated the effect of aspirin and dipyridamole on longer term clinical outcome.

Patients and method

Between 1978 and 1982, 320 consecutive patients were entered preoperatively into a randomised study to assess the effects on one year graft patency of aspirin and dipyridamole plus warfarin versus placebo plus warfarin. All 320 patients entered into

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the original study were considered for the clinical re-evaluation undertaken in the present study. Mortality was measured first. All patients undergoing coronary angiography (and thus coronary surgery) at the London Chest Hospital are "flagged" to allow return of any subsequent death certificates to the London Chest Hospital. The number of deaths during follow up could thus be recorded accurately.

Apart from five patients, who asked not to be contacted, all surviving patients were asked to attend an outpatient clinic, during a six month period in 1986. The outpatient interview was performed by one person who was unaware of the patient's original randomisation category. Information was documented on a standard questionnaire. The presence or absence of angina was determined, together with its severity (graded according to the Canadian Cardiovascular Society (CCS) classification), its time of onset after operation, and the use of antianginal medication (aspirin and dipyridamole plus warfarin or placebo plus warfarin). Patients were also asked how long they had taken their trial medication. We asked for information on admission to hospital for myocardial infarction. The hospitals were subsequently contacted for confirmation of myocardial infarction, with only electrocardiographic criteria or enzyme change being accepted as evidence. Work status before and after surgery was recorded. All patients were asked about their smoking habits.

Information on repeat angiography and reoperation during the follow up period was documented and the inpatient notes of these patients were reviewed to ascertain angiographic findings and reoperation details.

All patients were asked to undertake an exercise stress test according to the modified Bruce protocol. The test was stopped and regarded as abnormal if angina or ST segment depression >1 mm (80 ms beyond the J point) developed.

The preoperative left ventricular angiograms of all patients were visually analysed by classifying each of three wall segments (anterior, apical, and inferior) as normal or abnormal.

Results

MORTALITY

Thirty five of the original 320 patients died from the time of entry to time of reassessment (overall mortality 10.9%). Three died while waiting for an operation and seven died perioperatively (perioperative mortality 2.2%). Eight of the remaining 25 deaths were from non-cardiac causes. The 17 postoperative cardiac deaths occurred a mean of 37 months after operation and the average annual cardiac mortality was 0.8%. Fifteen (56%) of the 27

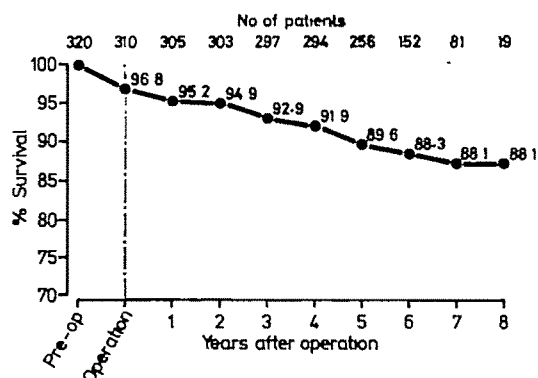


Fig 1 Cumulative survival curve.

cardiac deaths (preoperative, perioperative, and postoperative) were in patients with two or more abnormal segments on the preoperative left ventricular angiogram. Eighty nine (30.4%) of the 285 survivors had abnormal left ventriculograms ($p < 0.01$). Figure 1 shows the cumulative survival curve for all patients (deaths from cardiac plus non-cardiac causes).

Follow up patients

Two hundred and fifty (87.7%) of the 285 survivors attended the outpatient interview. Twenty eight of the 35 who did not reply had previously refused recatheterisation at one year. The mean time from operation to follow up interview was 6.6 years (range 4.3–8.6).

SYMPTOMS

Angina

Ninety four (37.6%) patients complained of recurrent angina but in only 23 (9.2%) was this severe (grade III or IV). Eighty five patients were taking antianginal medication including β blocking drugs in 52. In eight patients angina persisted despite a further operation. Figure 2 shows the cumulative incidence of angina.

Nine patients had had a myocardial infarction, which was confirmed by electrocardiogram or enzyme change in all cases.

Work status

Of the 250 patients interviewed, 205 (82.0%) were working before the operation. Twenty six (10.4%) reached retirement age during the follow up period and a further 35 (14.0%) failed to return to work either because they did not wish to or because they were retired on medical grounds. So 144 patients (56.8%) were in full time or part time employment a mean of 6.6 years after operation.

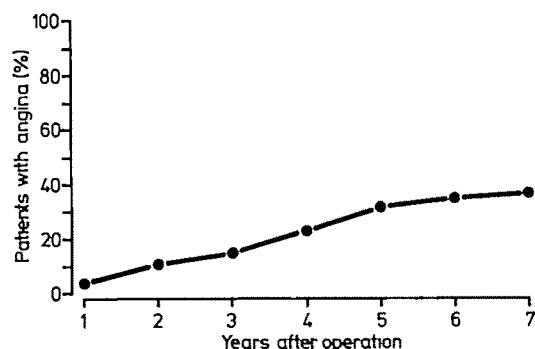


Fig 2 Cumulative incidence of angina.

Smoking

One hundred and fifty six (48.7%) of the original 320 patients smoked cigarettes before operation. Sixty six (26.4%) patients were smokers at the time of interview.

Reinvestigation

Twenty six (10.4%) of the 250 patients underwent repeat angiography for symptoms at a mean of 48 months (range 4–96) after operation. In these 26 patients 72 vessels had been grafted at operation and 38 (52.7%) grafts were found to be occluded or significantly stenosed. This compares with a graft occlusion rate of 13% at one year for all patients entered and a one year occlusion rate of 29% for these 26.

Reoperation

Reoperation was performed in 13 patients (twice in one patient) at a mean of 33.4 months (range 4–96) after the first operation. There were 34 original grafts, and at reinvestigation 22 (64.7%) grafts were occluded or severely stenosed. At reoperation 20 of these 22 originally grafted vessels were revascularised. In only two instances were grafts inserted into diseased vessels not originally grafted.

Exercise stress testing

Two hundred and eleven (84.4%) of the 250 patients were willing or physically able to perform an exercise test. Table 1 shows the results of the exercise tests.

There were 73 (34.6%) abnormal tests, 52 in the 94 patients with recurrent angina and 21 in the 117

Table 2 Clinical outcome in patients given aspirin and dipyridamole or placebo

	No	Aspirin and dipyridamole	Placebo	p
Patients interviewed	250	122	128	NS
Cardiac deaths	27	13	14	NS
Angina	94	49	45	NS
Myocardial infarction	9	7	2	NS
Ischaemic exercise test	73	39	34	NS
Repeat angiography	26	12	14	NS
Further operation	13	5	8	NS

patients without recurrent symptoms ($p < 0.001$). Six of the 13 patients who had undergone further surgery developed abnormal exercise tests.

EFFECT OF ASPIRIN AND DIPYRIDAMOLE ON LONG TERM CLINICAL OUTCOME

In the original study 160 patients were randomised to active treatment and 160 to placebo. One hundred and twenty two of the 250 patients interviewed at a mean of 6.6 years had been on active treatment for a mean of 25 months (range 0–63) and 128 had been on the placebo. All patients took warfarin for a mean of 3.2 months after the operation. Aspirin and dipyridamole conferred no significant clinical benefit at a mean of 6.6 years after operation (table 2). Ten patients died before receiving any medication; treatment was started on the second postoperative day.⁴ Of the 17 patients who died during the follow up period nine took aspirin and dipyridamole and eight took placebo (NS).

Discussion

Aortocoronary bypass grafting is an accepted form of treatment for patients with ischaemic heart disease. Much is known about the indications for, and natural history of, such grafts. The European study and the Coronary Artery Surgery Study indicated that surgery improves the outcome in certain groups. Follow up studies on graft patency suggest a failure rate of 10% in the first three months⁵⁻⁷ and an annual attrition rate of about 2.5% for the first five years and thereafter one of about 5% per annum.^{8,9}

Patients entered into the Veterans Administration Study between 1972 and 1974 were re-evaluated 11 years after the start of the study.¹⁰ At re-evaluation the survival rate was 58% for both medical and surgical groups; at seven years it was 70% and 77% respectively. Other studies have shown that the graft patency rate falls with time.^{8,9} Thus graft survival data and long term follow up data suggest that the benefits of vein grafting decrease significantly between seven and 11 years. Patients were entered into

Table 1 Exercise tests in 211 patients

		Ischaemic	Non-ischaemic
Recurrent angina	94	73 (34%) 52 (55%)	138 42
No recurrent angina	117	21 (18%)	96

these trials, however, before the development of a policy of total revascularisation in the late 1970s. There have been no long term British follow up studies in patients who have undergone total revascularisation. Additionally, since angioplasty is being increasingly used for the treatment of ischaemic heart disease, the longer term benefits of coronary surgery need to be restated.

The patients in the present study were recruited between 1978 and 1982. The perioperative mortality (2.2%) compares well with that of other studies. The work of Bourassa *et al* and Seides *et al*, who showed that progression of native disease was an important cause of new symptoms after vein grafting,^{11,12} led to the concept of total revascularisation. The present study started when total revascularisation was the practice at the London Chest Hospital. This may account for the favourable clinical outcome demonstrated at follow up study. At 6.6 years after operation 87.1% of patients were alive compared with 87% for the Coronary Artery Surgery Study at six years and 77% for the Veterans Administration Study at seven years. In our follow up, as in other studies, left ventricular dysfunction was a bad prognostic factor.

Recurrent angina developed in 37.6% of our patients, an average annual incidence of 5.7%. Only 9%, however, had severe symptoms and only 55.3% of their exercise tests were abnormal. Thus 205 (82%) patients were symptom free or had mild symptoms controlled with medication 6.6 years after operation. The policy of total revascularisation could account for these results as well as the frequency of subsequent infarction (3.6%) which is lower than that in other series ($\geq 13\%$).¹³

The proportion of patients working at a mean of 6.6 years after surgery is similar to that found in other studies,¹⁴ but the proportion of smokers was less, the result perhaps of improved patient education.

We cannot compare graft patency in this study with other long term follow up data because our patients underwent angiography only for symptoms. This means that our figure for early graft failure is likely to be an overestimate. But it is clear from the angiographic data obtained in those patients undergoing a second operation that the cause of recurrent symptoms was failure of the grafts rather than development of disease in new vessels. This confirms the value of total revascularisation at the time of first operation, as well as reaffirming the need for a better understanding of graft failure and its prevention.

There is evidence that the vein wall is damaged during grafting.¹⁵ Platelets adhere to damaged vessel walls.¹⁶⁻¹⁹ Platelets, activated as a result of deposition, release platelet derived growth factor²⁰ which causes the migration and proliferation of smooth muscle

cells. Beyond one year 2.5% of grafts are lost each year. The cause of this loss is likely to be hyperplasia of the intimal smooth muscle cells.²¹ The pathophysiological process described has led to attempts to prolong graft patency with the currently available antiplatelet drugs, aspirin and dipyridamole. Two studies have shown that aspirin improves early graft patency.^{22,23} There is no clear evidence, however, that aspirin and dipyridamole improve long term graft patency. The reported long term benefit from aspirin and dipyridamole²⁴ became non-significant when a Yates' continuity correction factor was applied to Cheseboro *et al*'s results.²⁴

Although aspirin limited the formation of thrombus in experimental vein grafts,²⁵ it did not prevent platelet adhesion or degranulation in response to strong stimuli such as collagen.²⁶⁻²⁹ These results may explain the lack of benefit of aspirin since intimal hyperplasia, the probable cause of long term graft failure,²¹ is the consequence of platelet adhesion. Alternatively, the failure of aspirin treatment may indicate that the role of platelets in late neointimal hyperplasia has been over-emphasised or that this process precedes the start of treatment.

The group of patients followed up in this study underwent repeat angiography at one year, and the use of aspirin and dipyridamole in addition to warfarin did not confer additional benefit over warfarin alone.⁴ Both of these regimens have a beneficial effect on thrombus formation. One criticism of the original study by Brookes *et al* was that aspirin and dipyridamole were not started until after operation. The difference between this study, with its lack of benefit, and Cheseboro *et al*'s study²⁴ was the high patency rate in Brooks *et al*'s placebo group, suggesting a benefit from warfarin. This would fit with the concept that early graft occlusion is the consequence of thrombus formation. The results for longer term clinical outcome presented now confirm that the addition of high dose aspirin and dipyridamole, taken for a mean of 25 months, does not confer longer term benefit. Additionally, it has been shown that there were significantly more gastrointestinal and bleeding complications in the group taking aspirin.⁴

The debate about aspirin dose continues. At the time the dose given to the patients in this study was thought to be appropriate. The beneficial effects of such a high dose on early graft occlusion, however, can be achieved with lower doses.³⁰ But we do not know if these high dose regimens also have a detrimental effect on prostacyclin production and the blood vessel wall interaction and hence no long term benefit on graft outcome.

Conclusions

We found a favourable clinical outcome in patients

entered into a British study in the late 1970s when surgery was performed according to current techniques. Symptoms after vein grafting were primarily caused by graft failure rather than new disease, confirming the need for total revascularisation. Additionally, the aspirin and dipyridamole results confirm those of Brooks *et al* in a one year follow up of these patients,⁴ indicating that, provided early thrombotic occlusion is prevented, these antiplatelet drugs confer no long term clinical benefit.

Current evidence suggests that coronary vein grafting is a good but palliative treatment for ischaemic heart disease. But because the patients in this study were entered at a time when total revascularisation was being undertaken routinely, it is important to continue to monitor them to see whether clinical outcome remains good. The problem of maintaining long term graft patency remains unresolved. A clearer understanding of the pathophysiology of graft failure and better antiplatelet drugs are needed.

We thank Dr N Brooks for allowing us access to the original data on these patients and Dr M Honey for allowing us to include his patients in the study.

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Gershlick, Lyons, Wright, Sturridge, Layton, Balcon

Neuroendocrine activation after acute myocardial infarction

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SUMMARY The extent of neuroendocrine activation, its time course, and relation to left ventricular dysfunction and arrhythmias were investigated in 78 consecutive patients with suspected acute myocardial infarction. High concentrations of arginine vasopressin were found within six hours of symptoms, even in the absence of myocardial infarction ($n = 18$). Plasma catecholamine concentrations also were highest on admission, whereas renin and angiotensin II concentrations rose progressively over the first three days, not only in those with heart failure but also in patients with no clinical complications. Heart failure, ventricular tachycardia, and deaths were associated with extensive myocardial infarction, low left ventricular ejection fraction, and persistently high concentrations of catecholamines, renin, and angiotensin II up to 10 days after admission, whereas in uncomplicated cases concentrations had already returned to normal.

The clinical presentation of acute myocardial infarction varies widely. Some patients have only mild constitutional upset, while others suffer intense vasoconstriction, arrhythmias, heart failure, or shock. In common with other major acute illnesses, myocardial infarction is accompanied by many metabolic and hormonal changes which may be related to the severity of illness and clinical outcome.¹ Although stimulation of neuroendocrine systems may be an appropriate response to acute myocardial injury, those hormones that promote vasoconstriction or tachycardia might also be harmful.

Of the vasoconstrictor mechanisms, catecholamine release has been the most extensively studied. Numerous reports have confirmed the initial observations in 1952 by Forssman² of raised concentrations of urinary³⁻⁵ and plasma⁶⁻⁸ catecholamines after myocardial infarction. High concentrations of catecholamines are frequently associated with the presence of heart failure, shock, or ventricular arrhythmias,^{4,7,8} and the potential for reducing infarct size and arrhythmias by interference with the catecholamine response by β blockers has attracted much interest.⁹⁻¹¹

Other vasoconstrictor hormones also may be important after myocardial infarction, and compared with catecholamines little is known of the role of the renin-angiotensin system. Preliminary observations indicate that concentrations of plasma renin are raised in some patients after myocardial infarction, particularly in association with heart failure, shock, or ventricular fibrillation.¹²⁻¹⁴ Furthermore, inhibition of angiotensin II formation in those with heart failure may confer haemodynamic benefit.^{15,16}

Nausea, vomiting, and administration of morphine^{17,18} may stimulate release of another potent vasoconstrictor, arginine vasopressin, but little is known about the activation of arginine vasopressin in this clinical setting. The vasoconstrictor effects of these neuroendocrine systems on the coronary and peripheral circulations may be mutually facilitatory,¹⁹⁻²¹ and they may have the potential to decrease myocardial and peripheral perfusion as well as lowering cardiac output.

We studied the extent and time course of the stimulation of the release of renin, angiotensin II, catecholamines, and arginine vasopressin in a large consecutive series of patients admitted to the coronary care unit with suspected myocardial infarction.

Patients and methods

We studied 78 consecutive patients with suspected

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acute myocardial infarction admitted to our coronary care unit within six hours of the onset of symptoms. We excluded those patients with a previous history of cardiac failure and those who were maintained on long term diuretic treatment, because neuroendocrine activation may have been present before the onset of acute myocardial infarction. We also excluded those with atrial fibrillation or frequent extrasystoles on admission because they were unsuitable for radionuclide ventriculography.

All patients included for study had a gated technetium-99m radionuclide scan performed on admission to measure the left ventricular ejection fraction (normal >45%), and venous blood samples were taken to measure the concentrations of plasma active renin (normal range 10–50 μ U/ml), angiotensin II (normal range 3–12 pmol/l), arginine vasopressin (normal range 0.3–0.7 pg/ml), adrenaline (normal range undetectable – 0.2 nmol/l), and noradrenaline (normal range 0.2–3.0 nmol/l). Plasma was separated within 15 minutes and frozen for assay later. To avoid the discomfort of repeated venepuncture we inserted an indwelling venous cannula. Venous blood sampling was repeated during bed rest on days 1, 2, and 3 after admission, and again after 30 minutes' supine rest on day 10. The diagnosis of acute myocardial infarction was based on standard electrocardiographic features on the serial electrocardiograms and on a significant rise of serum creatine kinase and its MB isoenzyme.

Clinical examination and chest x rays were performed on admission and at frequent intervals thereafter to detect the presence of heart failure. For the purposes of this study we defined clinical left ventricular failure as the presence of either basal crepitations or a third heart sound together with radiological pulmonary venous congestion sufficient to warrant treatment with frusemide. We made a note of the use of frusemide, which was the only diuretic used, and other drugs that might influence neuroendocrine activation during the period of study. Sustained ventricular tachycardia, symptomatic non-sustained ventricular tachycardia, and ventricular fibrillation were noted during routine monitoring in the coronary care unit over the first 48 hours.

Results

CLINICAL COURSE

Acute myocardial infarction was confirmed in 60 patients (mean (SEM) age 52.9 (1.2) years). Those patients in whom myocardial infarction was subsequently excluded acted as a control group for this study ($n = 18$, age 53.6 (1.9) years). Most of these patients were discharged from the coronary care unit on their second day; so for the control group there are

no data for day three. Thirteen patients (age 56.6 (1.9) years) with myocardial infarction developed clinical evidence of left ventricular failure during the study period, including two with cardiogenic shock. Four patients died during their hospital admission—one within 24 hours in cardiogenic shock, two with intractable left ventricular failure on days seven and 11, and one, who had previously had uncomplicated infarction, from late ventricular fibrillation on day 14.

Four patients had one or more episodes of ventricular fibrillation within 24 hours of admission. One of these patients died in cardiogenic shock, whereas the others subsequently had an uneventful clinical course. Two patients, one of whom was in heart failure, developed complete heart block on day four that required temporary cardiac pacing. In both cases, sinus rhythm had returned within 72 hours. Three patients who had no other clinical complications had atrial flutter or fibrillation in the first two days. Because these episodes lasted <1 hour, no treatment was given. Late ventricular tachycardia occurred in two patients, both of whom had sustained extensive myocardial damage with evidence of heart failure.

Satisfactory radionuclide scans were available for 69 of the 78 patients studied. In those with acute myocardial infarction left ventricular ejection fraction correlated inversely with the cumulative release of creatine kinase isoenzyme MB over the first three days ($r = -0.62$; $p < 0.001$). Mean (SEM) peak release of creatine kinase MB was higher (316.6 (42.1) U/l) in patients with left ventricular failure and ejection fractions were lower (23.3 (3.9)%) than in those without heart failure (192.5 (20.5) U/l and 33.5 (1.6)% respectively; both $p < 0.01$). In the control group the mean ejection fraction was 49.6 (2.8)%. On admission there were no significant differences in blood pressure between those with acute myocardial infarction and the control group. Although all groups showed a fall in blood pressure, those with left ventricular failure had significantly lower systolic pressures at day 2 than the control group (108 (4) mm Hg v 127 (3.4) mm Hg respectively; $p = 0.002$) and these differences were maintained at day 10.

Three patients who developed heart failure had been on β blockers that were stopped at admission. None of the patients with uncomplicated myocardial infarction was on β blockers at admission, and treatment with β blockers or diuretics was not started during the study period. Twenty patients without heart failure were given intravenous nitrates for a period of 24–48 hours because of persisting or recurrent cardiac pain without evidence of reinfarction. For those with clinical evidence of left ventricular failure during their admission the mean

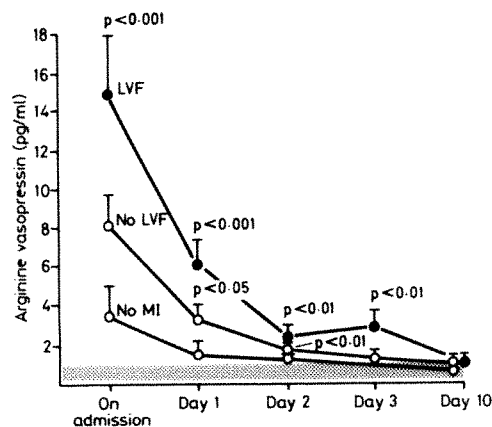


Fig 1 Changes (mean (SEM)) in arginine vasopressin concentration over 10 days in patients with heart failure (LVF), those without heart failure (no LVF), and those without myocardial infarction (no MI). Shaded area is normal range.

frusemide dosage at day 3 was 95 (22.7) mg. Figures 1-4 show the pattern of neuroendocrine activation for the control group and for those with myocardial infarction in the presence and absence of heart failure. Significance values were derived from Student's paired and unpaired *t* tests, and *r* values from Pearson's correlation coefficients.

ARGININE VASOPRESSIN

Concentrations of arginine vasopressin were highest at admission and declined rapidly over the next 48 hours (fig 1). In those with proven myocardial infarction, arginine vasopressin concentrations were

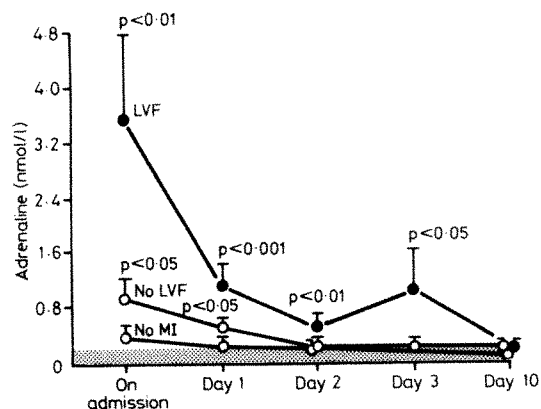


Fig 2 Changes (mean (SEM)) in adrenaline concentration over 10 days in patients with heart failure (LVF), those without heart failure (no LVF), and those without myocardial infarction (no MI). Shaded area is normal range.

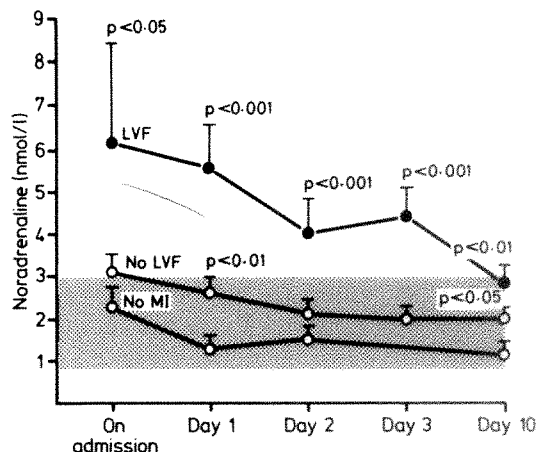


Fig 3 Changes (mean (SEM)) in noradrenaline concentration over 10 days in patients with heart failure (LVF), those without heart failure (no LVF), and those without myocardial infarction (no MI). Shaded area is normal range.

higher in 50 patients who were given narcotic analgesics before admission to the coronary care unit (range 0.15-39.98 pg/ml, median 7.19 pg/ml) than in 10 patients whose pain had spontaneously settled (range 0.17-2.92 pg/ml, median 1.31 pg/ml; $p = 0.007$). Arginine vasopressin concentrations also tended to be higher in the seven controls on narcotic analgesics (range 0.22-19.9 pg/ml, median 4.2 pg/ml) than in the eleven controls who did not require analgesia (range 0.02-16 pg/ml; median 1.41 pg/ml). This difference was not statistically significant. Ten patients required one or more further doses of diamorphine in the 12 hours before blood sampling on day 1, and although arginine vasopressin concentration had fallen significantly the median concentra-

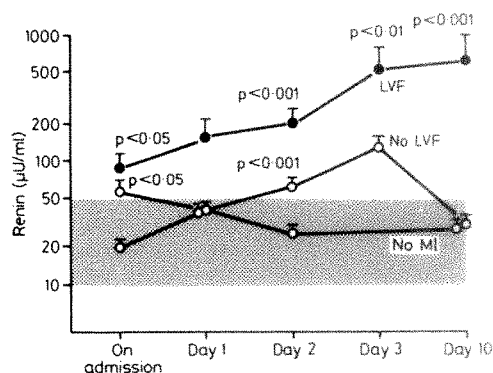


Fig 4 Changes (mean (SEM)) in renin concentration over 10 days in patients with heart failure (LVF), those without heart failure (no LVF), and those without myocardial infarction (no MI). Shaded area is normal range.

tion (3.63 pg/ml, range 0.3–9.9 pg/ml) was higher than in those ($n = 40$) who had analgesia only at or before admission (median 2.84, range 0.12–20.02 pg/ml; NS). In those with acute myocardial infarction, arginine vasopressin concentrations correlated with adrenaline concentrations on admission ($r = 0.57$, $p < 0.001$), but were only poorly correlated with the cumulative release of creatine kinase isoenzyme MB over the first three days ($r = 0.37$, $p < 0.01$). By day 10 mean concentrations of arginine vasopressin had returned almost to normal in all three groups of patients.

CATECHOLAMINES

On admission the mean plasma adrenaline concentration was raised in all three groups of patients. Plasma adrenaline concentration was significantly higher in those with heart failure (mean 3.54 (1.3) nmol/l, range 0.03–15.9) than in those without (0.96 (0.25) nmol/l, range undetectable – 7.4 nmol/l) and also in those in whom myocardial infarction was excluded (0.35 (0.05) nmol/l, range undetectable – 0.61 nmol/l). During the course of the admission all three groups showed a progressive decline in mean adrenaline concentrations towards normal (fig 2). Plasma noradrenaline concentrations also fell significantly during the course of the hospital stay in patients without heart failure and in the control group; in those without heart failure mean concentrations were just above the upper limit of normal on admission (3.12 (0.43) nmol/l (range 0.05–11.93 nmol/l), but they were within the normal range in the controls (2.34 (0.31) nmol/l) range 0.7–4.6 nmol/l). On admission mean plasma noradrenaline concentrations were at twice the upper limit of normal in patients with heart failure (mean 6.2 (2.3) nmol/l range 0.16–29.9 nmol/l), and high concentrations persisted over the next three days (fig 3). Correlations between heart rate and catecholamine release on admission were poor (adrenaline $r = 0.3$, noradrenaline $r = 0.4$), mainly because of the variability in heart rate in patients with inferior myocardial infarction. Catecholamine concentrations on admission, however, correlated with the cumulative release of creatine kinase MB (adrenaline $r = 0.46$, $p < 0.001$; noradrenaline $r = 0.39$, $p < 0.01$) and they also correlated inversely with ejection fraction (adrenaline $r = -0.42$, $p < 0.02$; noradrenaline $r = -0.53$, $p < 0.002$).

RENIN-ANGIOTENSIN SYSTEM

On admission mean plasma renin and angiotensin II concentrations were normal in the patients with myocardial infarction, but they rose by the third day to more than three times the upper limit of the normal range (203 (69) μ U/ml and 43.5 (8.6) pmol/l

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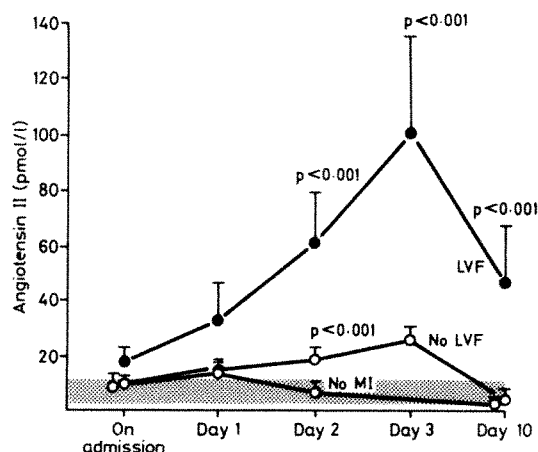


Fig 5 Changes (mean (SEM)) in angiotensin II concentration over 10 days in patients with heart failure (LVF), those without heart failure (no LVF), and those without myocardial infarction (no MI). Shaded area is normal range.

respectively). In the control group, mean concentrations of renin and angiotensin II remained normal throughout the study period, apart from a transient rise in angiotensin II on day 1 to 13.2 (3.5) pmol/l (range 1.9–48 pmol/l). Left ventricular failure was clinically present on admission in nine patients, and occurred later in four patients. Three patients had been treated with frusemide before blood sampling at admission (range 40–80 mg dose); plasma concentrations of angiotensin II were raised in only one. Two patients with cardiogenic shock and four patients with acute heart failure had not received diuretics; angiotensin II concentrations were raised in five of them. By day 3 the group treated for heart failure had high mean renin and angiotensin II concentrations (559 (303) μ U/l (range 95–3855 μ U/ml) and 102 (33) pmol/l (range 16–400 pmol/l) respectively). Renin and angiotensin II, however, also rose significantly in patients without heart failure in whom the mean concentrations were more than twice the upper limit of normal (104 (14) μ U/l (range 4–455 μ U/ml) and 26.8 (3.3) pmol/l (range 1–90 pmol/l) respectively) at the third day. This included high angiotensin II concentrations in 16 of 27 patients who had received no drug treatment other than analgesia on admission to hospital. By day 10, renin and angiotensin II concentrations had returned to normal in patients without heart failure, but high concentrations continued in most of those treated for persistent heart failure (figs 4 and 5). The table shows the angiotensin II concentrations in all 13 patients with heart failure and their respective diuretic dosages. Renin and angiotensin II concentrations correlated well on admission ($r = 0.56$), at day 3 ($r = 0.83$), and at day

Table Individual angiotensin II concentrations (pmol/l) and frusemide dosage (mg) over the previous 24 hours in patients with heart failure. Shading indicates presence of clinical heart failure

Case No	OA	F	Day 1	F	Day 2	F	Day 3	F	Day 10	F	Outcome
1	50.0	0	126.0	80	124.0	160	132.0	200	100.0	160	Cardiogenic shock
2	34.4	0	Died								Cardiogenic shock
3	15.2	0	8.1	80	41.0	80	52.0	80	66.0	80	Severe failure
4	26.0	0	30.8	160	157.1	240	255.0	240	Died		Severe failure
5	14.0	0	20.0	0	65.0	160	78.0	200	180.0	160	Severe failure—died
6	30.0	0	140.0	80	200.0	160	400.0	80	33.2	80	Moderate failure
7	3.6	80	2.2	80	9.8	80	16.2	80	10.5	80	Moderate failure
8	3.2	40	20.0	40	29.7	40	29.0	80	29.7	40	Moderate failure
9	16.6	0	14.8	40	55.2	80	68.6	80	3.9	40	Moderate failure
10	4.1	0	3.7	0	10.0	40	35.0	80	45.0	40	Moderate failure
11	7.2	0	14.0	80	18.0	0	75.0	0	3.1	0	Mild failure
12	25.0	80	22.0	0	28.0	0	48.0	0	12.0	40	Mild failure
13	3.5	0	11.4	0	16.9	0	32.1	20	7.0	40	Mild failure

OA, on admission; F, frusemide.

10 ($r = 0.80$) ($p < 0.001$). Renin on admission correlated with catecholamines (adrenaline, $r = 0.59$, $p < 0.001$; noradrenaline, $r = 0.37$, $p < 0.01$) and also with peak creatine kinase MB ($r = 0.43$, $p < 0.001$). We found no significant correlations between concentrations of arginine vasopressin or ejection fraction and activation of the renin-angiotensin system.

RELATIONS WITH ARRHYTHMIAS AND DEATH

Ventricular fibrillation occurred in four patients within the first 24 hours. Three had normal noradrenaline concentrations and only mildly raised adrenaline concentrations on admission. This included one patient in whom ventricular fibrillation developed during blood sampling (adrenaline 0.21 nmol/l, noradrenaline 3.01 nmol/l). They subsequently had an uneventful recovery. The fourth patient was in cardiogenic shock and died within 24 hours. Angiotensin II concentration on admission was markedly raised in this patient (34.4 pmol/l), as were adrenaline (4.4 nmol/l) and noradrenaline (3.4 nmol/l).

Three other patients died in hospital. Two had progressive intractable heart failure with high angiotensin II and noradrenaline concentrations at day 3. The clinical condition of the third patient had been uncomplicated despite a low ejection fraction (13%) and he died on day 14 from late ventricular fibrillation. At day 10 he had raised catecholamine concentrations (adrenaline 0.45 nmol/l, noradrenaline 7.7 nmol/l) and also high angiotensin II (17 pmol/l).

Two patients with symptomatic episodes of ventricular tachycardia had very high catecholamine concentrations on admission (adrenaline 1.25 and 7.44 nmol/l, noradrenaline 6.43 and 6.15 nmol/l) and raised angiotensin II concentrations (15.2 and 25 pmol/l). Furthermore, both of these patients had low

left ventricular ejection fractions (7% and 22%), although only one had clinical signs of heart failure. Atrial flutter and fibrillation were seen in two patients with inferior myocardial infarction, and these were not associated with raised catecholamine concentrations. Late ventricular tachycardia occurred in a further two patients, both of whom had been treated for heart failure and had persistently high catecholamine and angiotensin II concentrations at day 3.

Thus in this small group of patients with arrhythmias, primary ventricular fibrillation was not closely related to the magnitude of neuroendocrine activation, although episodes of ventricular tachycardia on admission were accompanied by very high catecholamine concentrations. Late life threatening ventricular arrhythmias and deaths occurred only in those with major left ventricular dysfunction, which was also associated with persistently high catecholamine and angiotensin II concentrations.

Discussion

This study describes for the first time in a large consecutive series the extent, time course, and interrelations of neuroendocrine activation after acute myocardial infarction. Although raised urinary aldosterone had been noted as early as 1956,²² the role of the renin-angiotensin system after myocardial infarction has been neglected until recently. Preliminary studies measuring renin show a very wide range of individual responses. Vaney *et al* described raised renin and catecholamine concentrations on admission in 19 patients with acute myocardial infarction; concentrations were highest in four of eight patients who subsequently developed cardiogenic shock or ventricular fibrillation.¹² Wenting *et al*, however, found normal renin concentrations in four patients with heart failure within 12 hours of



acute myocardial infarction in the absence of diuretic treatment, although high renin concentrations were seen at 48–72 hours in two other patients who received inotropes and vasodilators.¹⁵ A much larger study by Michorowski and Ceremuzynski of 95 patients showed raised renin concentrations in 20 of 22 patients within six hours of chest pain in the presence of heart failure, arrhythmias or shock, but no significant increase in patients without clinical complications.¹⁴

These findings are extended and confirmed in our study, in which most patients had normal concentrations of renin and angiotensin II within six hours of symptoms, with the exception of those with severe heart failure or shock. Sequential measurements in patients without clinical complications, however, showed a significant increase in renin and angiotensin II by day 3, in the absence of treatment with vasodilators or diuretics. Those treated for heart failure had very much higher angiotensin II concentrations at day 3, which persisted at ten days and presumably for longer.

Stimulation of renin secretion during the first three days after myocardial infarction is likely to be dependent on several interacting variables. The initially very high arginine vasopressin concentration may have suppressed renin release,^{23,24} whereas acute reduction in renal blood flow, together with increased renal nerve activity may stimulate the renin-angiotensin system.^{25,26} There seems little doubt that contraction of blood volume associated with diuretic treatment contributed to the extremely high concentrations of renin and angiotensin II in those with heart failure, but concentrations of these hormones were raised on admission in nearly half of this group before diuretic treatment. We confirmed previous observations of a relation between catecholamines and initial renin concentration,¹⁴ which suggests that this may be one of the more important initial stimuli to renin secretion in this clinical setting.

As shown previously,^{4,7,8} catecholamine release was also related to the extent of left ventricular damage as assessed by cardiac release, ejection fraction, and the presence of heart failure. Whether catecholamines have any direct influence on infarct size remains uncertain, but raised urinary and plasma catecholamine concentrations have been reported to be related to the frequency of early ventricular arrhythmias.^{4,5} In our study only six out of 60 patients had ventricular fibrillation or haemodynamically important ventricular tachycardia in the first 24 hours, and short salvos of ventricular extrasystoles were not documented. β Blockade at an early stage when catecholamine concentrations are highest seems a logical tactic both to reduce arrhythmias and limit the

extent of infarct damage, and this has been the focus of several studies.^{9–11} In our study, however, catecholamine concentrations were highest in a group in whom β blockers are generally contraindicated—that is those patients in whom heart failure is developing.

Arginine vasopressin release during acute myocardial infarction has received little attention. We found markedly raised arginine vasopressin concentrations at admission, not only in those with myocardial necrosis but also in some patients in whom myocardial infarction had been excluded. Furthermore, the correlation between arginine vasopressin concentrations and creatine kinase release was poor, suggesting that factors other than myocardial necrosis are responsible for arginine vasopressin release. Administration of morphine was strongly associated with the considerable increase in arginine vasopressin in both those with myocardial infarction and in the control group. In contrast, in patients with myocardial infarction who were not given morphine arginine vasopressin was only slightly raised, and this is also true of the control patients who did not receive morphine. Thus after myocardial infarction arginine vasopressin is more likely to be high as a result of treatment than as a primary response to acute myocardial infarction. The explanation for the correlation between initial concentrations of adrenaline and arginine vasopressin might also be that those under greater stress because of pain or nausea and vomiting had received higher doses of morphine.

The antidiuretic effect of arginine vasopressin is well recognised and probably contributes to the low urine volumes in the first 24 hours after myocardial infarction. It has been estimated that approximately 760 ml water is gained then.²⁷ Although infusion of arginine vasopressin does not raise blood pressure, except in very high concentration (100 ng/l),²⁸ it is an extremely potent arterial vasoconstrictor. Arginine vasopressin has been given as a provocative test for angina and coronary artery spasm,²⁹ and in other situations in which there is an excess of arginine vasopressin, myocardial infarction, arrhythmias, and sudden death have been reported.^{30–32} We do not know whether the concentrations of arginine vasopressin seen after myocardial infarction in this study had important haemodynamic effects, but the vasoconstrictor properties of arginine vasopressin may be enhanced by noradrenaline, and both of these hormones were at their highest in the first 24 hours after admission.

The interaction of raised plasma concentrations of angiotensin II, arginine vasopressin, and catecholamines could be harmful in several ways. Arginine vasopressin, noradrenaline, and angiotensin II are potent arterial vasoconstrictors that could increase left ventricular afterload and lower coronary

perfusion. Similarly tachycardia and arrhythmias induced by catecholamine excess could be disadvantageous. Furthermore, the combination of vasoconstriction mediated by these hormones and volume expansion through the sodium retaining effects of increased renal sympathetic nerve activity, stimulation of aldosterone secretion, and antidiuresis in the presence of raised arginine vasopressin concentration provides the setting for the development of acute heart failure. Treatment with angiotensin converting enzyme produced short term and long term haemodynamic improvements in patients with chronic heart failure.³³⁻³⁵ Inhibition of angiotensin II production in chronic heart failure has also been associated with reduction of arrhythmias,³⁶ a significant rise in body potassium,³⁷ and a reduction in plasma catecholamine concentrations.^{36,37} More recently beneficial haemodynamic changes have been shown with angiotensin converting enzyme inhibitors in heart failure complicating myocardial infarction.^{15,16,38} These findings suggest that clinical trials of early intervention with angiotensin converting enzyme inhibitors in patients with extensive myocardial infarction and heart failure should be considered.

In addition to these more obvious adverse haemodynamic consequences, neuroendocrine activation could have other subtle effects on myocardial structure and function. Experimentally, high concentrations of catecholamines and angiotensin II cause diffuse microscopic myocardial cellular necrosis in rabbits, and in man can cause similar lesions even in the absence of coronary disease.³⁹ Recent studies show that infarct expansion and progressive ventricular dilatation occur in some patients after myocardial infarction.⁴⁰⁻⁴² In animal models angiotensin converting enzyme inhibitors may reduce infarct size,⁴³⁻⁴⁵ increase collateral blood flow to the infarct zone,⁴³ reduce the incidence of reperfusion arrhythmias,⁴⁶ and through improved ventricular remodelling in rats⁴⁷⁻⁴⁹ can lead to an increase in survival.⁴⁶

Thus persisting high concentrations of angiotensin II after myocardial infarction could have important implications not only for the development of acute heart failure, but also for long term cardiac structure and function. The observations reported here provide a logical basis for the cautious exploration of the effects of angiotensin converting enzyme inhibition given early in acute myocardial infarction on ventricular structure and function.

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Evidence of the inaccuracy of standard echocardiographic and angiographic criteria used for the recognition of true and "false" left ventricular inferior aneurysms

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SUMMARY Diagnosis of so-called false aneurysms of the left ventricle after infarction is judged to be important because the risk of rupture is high and resection of aneurysms with a narrow orifice is usually successful. Aneurysms with larger communication orifices are less likely to rupture. Echocardiographic and angiographic criteria have been devised to classify left ventricular aneurysms into two distinct types. In four cases of inferior aneurysms the echocardiographic and angiographic criteria were typical of a "false aneurysm" but the defects were diagnosed as true aneurysms after intraoperative and histological examination. These aneurysms were characterised by their site in the inferior wall and by late diagnosis and treatment, which may have influenced their occurrence and determined the development of their characteristic shape.

These findings suggest that the classic echocardiographic and angiographic diagnostic criteria for "false" aneurysms may have to be abandoned.

Left ventricular aneurysms with narrow communication orifices are more likely to rupture than aneurysms with wider necks. In 1975 Roelandt *et al* established echocardiographic criteria to differentiate between so-called false and true aneurysms.¹ Angiographic² and anatomical criteria³ have also been developed. The four patients we report had an inferior left ventricular aneurysm that developed after myocardial infarction; their echocardiographic and angiographic features were in every respect those that are regarded as being characteristic of a "false" aneurysm. At operation and histological examination, however, these so-called false aneurysms were found to be "true" aneurysms.

These findings suggest that the classic diagnostic criteria for "false" aneurysms may have to be abandoned, at least for inferior aneurysms.

Case report

All four patients had an acute myocardial infarction as the first sign of coronary artery disease. Diagnosis of myocardial infarction was delayed (12 hours to 2 months), mean 18 days after the onset of chest pain. This implied that there had been a long delay before bed rest and treatment were started (more than three days in three patients). The electrocardiogram indicated an inferior or inferolateral transmural infarction in all instances. All the patients had symptoms (congestive heart failure (two patients), angina pectoris (one patient), or palpitation related to ventricular extrasystoles (one patient)). Echocardiographic examination (Roche-Kontron RT 400 or Diasonics CV 4000) showed an inferior or inferolateral aneurysm in every patient between the mitral annulus and one of the papillary muscles, that was typical of a false aneurysm (fig). The following features were present: (a) evidence of a narrow orifice between the left ventricular chamber and the "aneurysm"; (b) at the end of systole the internal diameter of the orifice (O max) was much smaller than the maximal internal diameter (D max) of the aneurysmal sac and a ratio O max/D max was much

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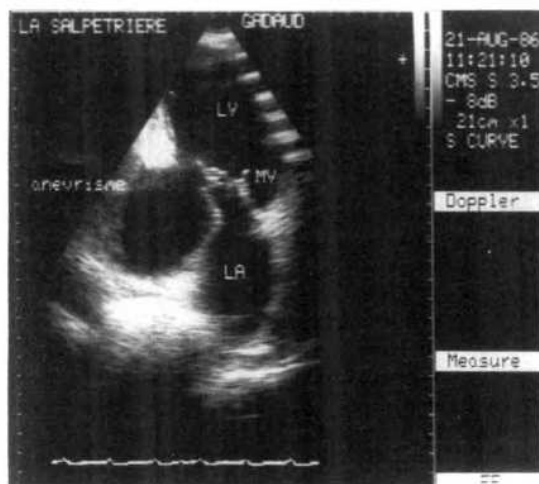


Figure An apical two chamber echocardiogram showing an aneurysm of the inferior left ventricle. LV, left ventricle; LA, left atrium; MV, mitral valve.

less than one; (c) the "aneurysm" was saccular and there was an acute angle between the aneurysmal wall and the ventricular wall.^{4,6} The expansion of the aneurysmal formation in systole is not usually regarded as being specific.^{4,6} The best echographic views for imaging the aneurysmal sac were the apical two chamber and subxiphoid four chamber. Left ventricular function was depressed in all the patients, with a fractional shortening of less than 26% (20–26%). The end diastolic diameter was also abnormal (60–70 mm). Angiographic data were consistent with the echocardiographic data and also suggested evidence of a false aneurysm^{4,7} (table). The table also shows other angiographic findings. The four patients were operated on because of their symptoms and because they were thought to have a false aneurysm.

Table Haemodynamic and angiographic data

Data	Patient 1	2	3	4
Site	Inf	Inf	Inf lat	Inf
EF	0.39	0.25	0.37	0.28
LVEDP (mm Hg)	16	11	10	19
EDV (ml/m ²)	143	148	91	283
ESV (ml/m ²)	87	110	57	204
An EDV (ml/m ²)	139	8	31	104
An ESV (ml/m ²)	151	14	41	70
O max/D max	0.38	0.60	0.67	0.49
Coronary arteries (% stenosis)	Cx 100%	RCA 100% LAD 75%	Cx 100% RCA 90%	Cx 100%

EF, ejection fraction; LVEDP, left ventricular end diastolic pressure; EDV, end diastolic volume; ESV, end systolic volume; An EDV, aneurysm end diastolic volume; An ESV, aneurysm end systolic volume; Cx, circumflex artery; RCA, right coronary artery; LAD, left anterior descending artery.

But the intraoperative and histological findings were typical of a true aneurysm according to several criteria. At operation a true aneurysm has a circumscribed area of scar tissue which is thin and often adherent to the pericardium. In this area elements of the original wall can be identified and the area may or may not bulge paradoxically in systole.^{4,6,9} Histologically a so-called true aneurysm is characterised by the presence of myocardial cells and coronary vessels in the aneurysmal wall.³

The aneurysms were resected in all four patients; one patient also had coronary artery bypass grafting. After at least one year of follow up all the patients were in New York Heart Association functional class I or II without angina.

Discussion

The diagnostic criteria for true and false aneurysms have been developed and are now routinely used.^{1,4,6} These criteria were derived from small series of patients.^{1,4,6} None of these series had more than five patients with a false aneurysm. Diagnoses were usually based solely on echocardiography and angiography because few patients had a surgical and histological examination. In our four patients the echocardiographic and angiographic findings were typical of a "false" aneurysm but true aneurysms were found at operation. Neither the width of the communication orifice, the ratio O max/D max, nor the angle between aneurysm wall and ventricular wall could reliably distinguish between the two types. It is possible that these criteria cannot be applied to lesions at inferior or inferolateral sites; these have not been extensively studied because they are so rare. Two features can be recognised as typical of inferior true aneurysms. Firstly, they occurred after late diagnosis therefore delaying initiation of bed rest and treatment. To our knowledge this potentially predisposing factor has not been identified previously. Secondly, an inferior infarction is located between two resistant structures—the mitral annulus and the papillary muscle—and if the wall stress is large enough an aneurysm may develop but its orifice will necessarily be narrow.

In conclusion, the present study clearly shows that the present criteria that are used to differentiate between so-called true and false aneurysms should be reconsidered, particularly in the case of inferior or inferolateral aneurysms.

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Hour-glass deformity of the pulmonary valve: a third type of pulmonary valve stenosis

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SUMMARY In the 12 years from 1975 to 1987, 55 patients had open pulmonary valve surgery for isolated congenital stenosis of the pulmonary valve. Three types of pulmonary stenosis were seen: (a) dome-shaped pulmonary stenosis (34 patients); (b) dysplastic pulmonary valves with thick cauliflower-like cusps (12 patients), and (c) hour-glass deformity of the pulmonary valve, with "bottle-shaped" sinuses (nine patients). This third type has not been described before.

Preoperative identification of the valve structure is important because the choice of treatment (balloon dilatation for some dome-shaped valves and excision for dysplastic and hour-glass valves) depends on the type of stenosis.

Isolated pulmonary valve stenosis is the most common cause of right ventricular outflow tract obstruction and accounts for 8-10% of all congenital cardiac anomalies.¹ It was first described by Morgagni in 1761, and Meckel reported anatomical features in 1817.²

In the most common form of stenosis, the pulmonary valve is conical as a result of fusion of the valve leaflets, and it protrudes superiorly into the pulmonary artery. Its shape and opening are influenced by the degree of thickness and rigidity of the fused cusps. Its appearance on angiography has led to the descriptive term dome-shaped pulmonary stenosis. In another type of pulmonary stenosis fusion of the commissures is slight, but there is considerable obstruction to flow caused by noticeably thickened, immobile cusps composed of disorganised myxomatous tissue; this distinctive type of pulmonary stenosis is associated with a rather narrow valve annulus and has been termed "pulmonary valvular dysplasia."^{3,4} Patients with Noonan's syndrome have pulmonary valves of this type.⁵

We report a third type of pulmonary valve deformity, which, because of its angiographic appearance,

we have called hour-glass deformity of the pulmonary valve with bottle-shaped sinuses.

Patients and methods

Between 1975 and 1987, 55 patients (30 male and 25 female, aged from 6 weeks to 32 years) had open pulmonary valve operation for isolated stenosis in the Department of Thoracic and Cardiovascular Surgery at the Sheba Medical Centre and the Department of Cardiac Surgery at the Rambam Medical Centre. Isolated pulmonary valve stenosis was diagnosed by clinical, electrocardiographic, and Doppler echocardiographic criteria and was confirmed by cardiac catheterisation and right heart angiography. We also used the criteria of Koretzky *et al*³ and the radiographic features of Jeffrey *et al*⁴ to identify dysplastic valves.

Operation was indicated if the right ventricular systolic pressure was >75 mm Hg and there were electrocardiographic signs of severe right ventricular hypertrophy. The preoperative identification of cauliflower or hour-glass valves improved as we became more experienced in interpreting the angiograms.

The pulmonary valve was examined during operation; the structural characteristics were noted, including thickness and type of the cusps, degree of commissural fusion, form of the valve sinus, and the effective size of the valve orifice.

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We did not study patients with bicuspid valves, unicuspid valves, and valves with little or no commissural development. We focused on the different structural types of abnormalities of the tricuspid pulmonary leaflets.

All patients are being followed clinically, radiographically, electrocardiographically, and echocardiographically for long term assessment.

Results

We identified three distinct structural types of pulmonary valve stenosis under direct vision during operation:

THE DOME-SHAPED VALVE (FIG 1B)

Thirty four of the 55 patients had pulmonary stenosis caused by a dome-shaped valve. The commissures were fused and their ridges extended towards the centre of the valve (fig 2a).⁶ The sinuses were moderately deep and wide open from commissure to commissure. The cusps were thicker than normal, but smooth on both sides. The valve orifice was usually round and central. The angiographic picture (fig 2b) clearly showed that the stenotic pulmonary valve was dome-shaped. The diameter of the pulmonary artery at the level of the commissures was normal and neither enlarged nor narrowed. Post-stenotic dilatation of the main pulmonary artery increased with age. None of the 34 patients with dome shaped pulmonary stenosis showed features of Noonan's syndrome.⁵

These patients were treated by commissurotomy extending to the arterial wall, with unhinging of the cusps for better mobilisation. Balloon dilatation, first described by Kan *et al*⁷ in 1982 and subsequently reported by others,⁸⁻¹⁰ should now be considered as an alternative treatment in patients with a dome-shaped valve.

THE DYSPLASTIC PULMONARY VALVE (FIG 1C)

Twelve patients had dysplastic valves (fig 1c) with thick, cauliflower-like cusps. The firm and verrucous tissue and the uneven distribution of the residual primitive myxomatous material of the cusps obstructed the flow through the pulmonary valve. There was either little or no fusion of the commissures, but the valve sinuses were to a large extent occupied by the dysplastic material of the cusps, making it difficult for them to deviate laterally in systole and allow unobstructed forward blood flow. None the less, the sinuses were well developed with wide open orifices (fig 3a). Once we knew what to look for, this type of valve was easily recognised on angiography (fig 3b) and verified on operation. Various grades of post-stenotic dilatation were present in these patients,

both on angiography and at operation, while at the valve level the pulmonary artery showed no particular changes.

In our first operation on this type of valve, in 1975, we performed partial cusp resection and trans-valvar patching. This approach was not satisfactory, and we found that complete removal of all the obstructing material within the valve by partial or complete valvectomy allowed free flow into the pulmonary system. There was no need for additional trans-valvar patching, as the obstruction was at the level of the cusps rather than the annulus.

All patients with Noonan's syndrome had valves of this type, but the reverse was not true.

HOOR-GLASS DEFORMITY OF THE PULMONARY ARTERY WITH BOTTLE-LIKE VALVE SINUSES (FIG 1D)

Nine patients presented with this newly described type of stenosis. Patients showed varying degrees of post-stenotic dilatation of the pulmonary artery, distal to the plane of the commissures and orifice. At

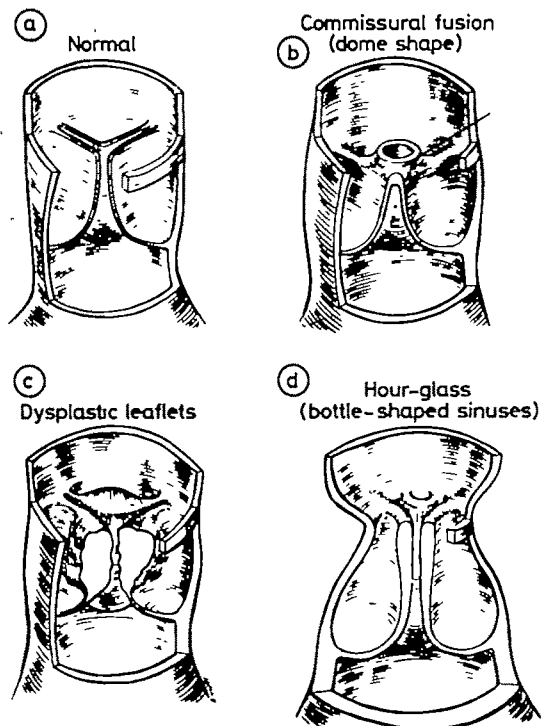


Fig 1 Appearance in diastole of normal pulmonary valve (a), dome-shaped pulmonary stenosis (b), dysplastic pulmonary valve with cauliflower-like cusps (c), and hour-glass deformity of the pulmonary artery with deep bottle-like sinuses (d).

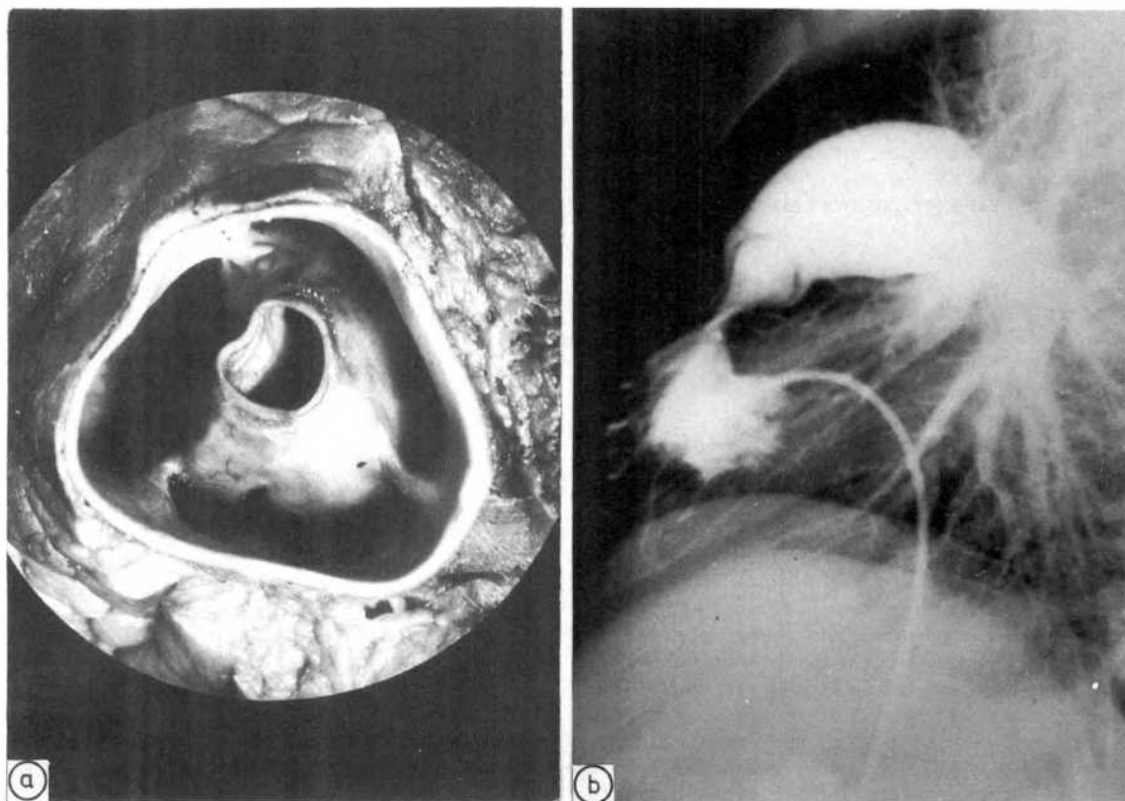


Fig 2 Photograph of a dome-shaped stenotic pulmonary valve showing (a) fusion of the commissures resulting in a funnel with an almost circular valve orifice (reprinted with permission from Parker⁶). Note the wide orifices of the sinuses. (b) Angiogram (lateral view) in end systole. Fusion of the three cusps gives the appearance of a dome.

this level the pulmonary artery was narrower than it was at its origin from the right ventricular outflow tract or at the post-valvar segment, and thus it resembled an hour-glass (fig 1d). The commissures were either not fused or only slightly fused. The cusps were thicker than those of the dome-shaped valves, but their surface was smooth on both sides; the outflow edges were thickened and rolled in towards the valve sinuses, forming relatively narrow, asymmetrical orifices to each. The pulmonary artery at the level of the commissures and orifice was markedly thickened, with a ring of sinus and orifice tissue on its inner side (fig 1d). This was soft in the younger patients and firm and scar-like in older patients. The sinuses resembled bottles, being deep and dilated with narrow orifices (fig 4a). The valve outlet was obstructed both by the hour-glass deformity and by the thickened cusps and their rolled-in edges. Preoperative diagnosis of hour-glass deformity

could be made angiographically by recognition of the narrowing at the plane of the commissures and orifice and by the bottle-like sinuses on a right ventricular angiogram (fig 4b).

We tried both commissurotomy and partial valve resection before we found that total pulmonary valvectomy was the most successful treatment. Trans-valvar patching was not required, because the pulmonary artery was widened sufficiently by relief of the inward tension at the level of the sinus orifices.

None of the 55 patients died nor were there major complications.

Discussion

Congenital pulmonary valve stenosis includes both the well-known dome-shaped pulmonary stenosis and the more recently described dysplasia of the pulmonary valve,^{3,4} with its special relation to Noon-

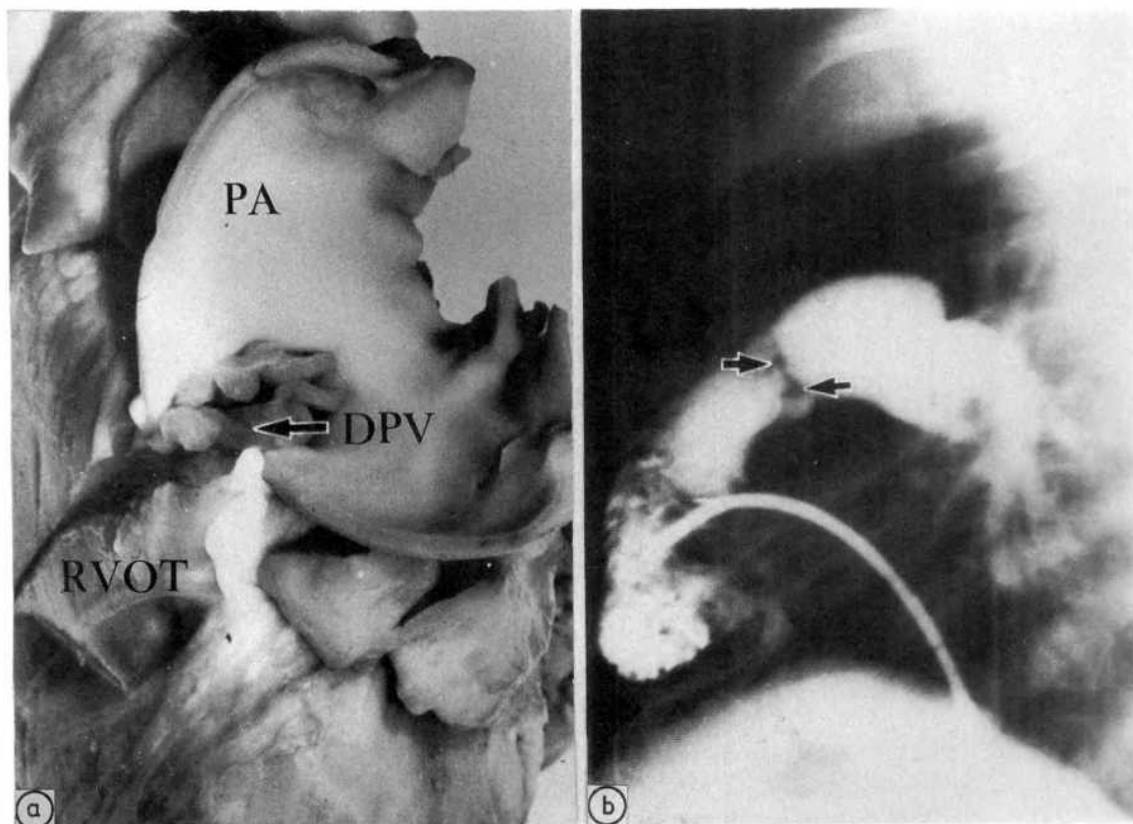


Fig 3 Photograph of a dysplastic pulmonary valve (DPV) showing the cauliflower-like cusps. The commissures are not fused. The sinus orifices are wide. The obstruction to flow in this valve is caused by excess dysplastic tissue. There is considerable post-stenotic dilatation of the pulmonary artery (PA). RVOT, right ventricular outflow tract. (b) Angiogram (lateral view) after injection of contrast into the right ventricle. Irregular filling defects (arrows) of contrast material at the valve level indicate smooth, thicker than normal, cauliflower-like masses on the cusps, that obstruct flow through the valve. There is considerable post-stenotic dilatation.

an's syndrome.⁵ In the present study we found a third form of pulmonary stenosis, the hour-glass pulmonary stenosis, which, to our knowledge, has not been recognised before. Koretzky *et al*, who described dysplasia of the pulmonary valve in 1969, found supra-valvar pulmonary stenosis in two of their six specimens.³ Jeffrey *et al* described the radiographic features of supra-valvar pulmonary stenosis and presented cases in which there was pronounced annular hypoplasia and valve thickening.⁴ Their case 10 demonstrated bottle-like sinuses in diastole. Among patients operated on for isolated pulmonary stenosis, Utley and Roe described one case in which the stenosis of the valve was associated with narrowing of the proximal pulmonary artery at the distal attachment of the valve cusps.¹¹ We believe that these

workers described the narrowing at the plane of the commissures and orifice that we saw in hour-glass deformity.

We used the term hour-glass deformity of the pulmonary valve to describe both the external and internal shape of the malformation; it has its own distinct features and its own relevance to surgical repair.

The structure of these three types of pulmonary stenosis can be identified by angiography: (a) doming of the valve (fig 2) is the usual finding in pulmonary stenosis; (b) filling defects at the valve level (fig 3) as well as irregular thickening of the cusps are highly suggestive of dysplastic pulmonary valve with cauliflower deformation of the cusps, while (c) narrowing at the distal cusp level with deep

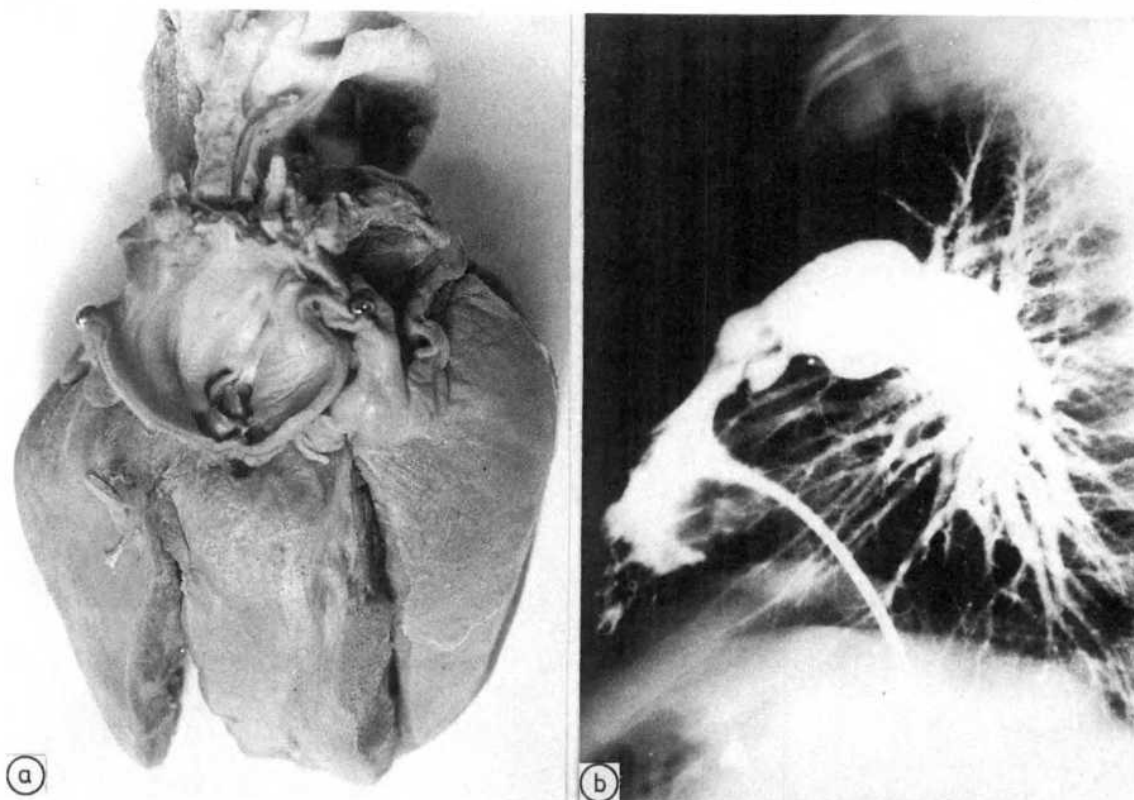


Fig 4 (a) Photograph showing hour-glass deformity of the pulmonary valve. The commissures are not fused. The orifices of the three sinuses are very narrow (bottle-necks). Distal to the commissure-orifice plane, there is considerable post-stenotic dilatation of the pulmonary artery. (b) Angiogram (lateral view) of end systole showing the hour-glass deformity of the pulmonary artery and the bottle-shaped sinuses. The filling defects at the valve level indicate smooth cusps. There is considerable post-stenotic dilatation of the pulmonary artery.

“bottling” of the sinuses (fig 4) indicates hour-glass pulmonary stenosis.

Radiographic and direct surgical examination showed various degrees of post-stenotic dilatation of the pulmonary artery in all types of pulmonary stenosis. We found that the degree of post-stenotic dilatation depended not on the type of valve obstruction, but rather on its duration and severity. Others, however, found post-stenotic dilatation only with dome-shaped valves.^{14,12}

Preoperative diagnosis of the type of pulmonary valve stenosis is important. Only the most common type, the dome-shaped valve, is structurally amenable to simple balloon dilatation or to the double balloon technique recently reported by Al Kasab *et al*,¹³ which eliminate the need for surgery. Although it may seem reasonable to assume that, as with surgical intervention, balloon dilatation results in valvotomy along the fused commissures, this has not

yet been shown to be the case. Unfortunately, the balloon technique is less satisfactory when combined infundibular and pulmonary valve stenosis are present¹⁴ or when the valve is either of the cauliflower^{15,16} or of the hour-glass type, because fused commissures are not the major problem in these two types. Patients with dysplastic cauliflower valves are most likely to benefit from excision of the obstructive cusps. In patients with the hour-glass valves excision of the cusps frees the constriction of the sinuses and allows the valve to dilate to nearly its physiological diameter at the commissural level thus eliminating any need for transvalvar patching.

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Assessment of the severity of mitral regurgitation from the dynamics of retrograde flow

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SUMMARY Sixty four consecutive patients with isolated mitral regurgitation referred for Doppler echocardiography were divided into three groups: group 1, 20 patients with severe mitral regurgitation that required operation; group 2, 22 patients with severe left ventricular dysfunction and secondary mitral regurgitation; and group 3, 22 patients with mild to moderate mitral regurgitation that did not require valve operation. M mode and continuous wave Doppler traces with a simultaneous electrocardiogram and phonocardiogram were analysed to identify time intervals that could be used to distinguish patients who needed valve operation from those who did not. An interval of < 55 ms between the aortic component of the second heart sound (A_2) and the cessation of mitral retrograde flow was a powerful predictor that the patient required operation (sensitivity 100% and specificity 86%). The mean (SD) value of this variable in group 1 (40 (15) ms) was significantly lower than in group 2 (90 (35) ms) and group 3 (75 (20) ms). Mean isovolumic relaxation time was less than normal in group 1 but did not differ significantly between groups. Deceleration of regurgitant velocity at end ejection was greater in group 1. The pressure drop from the left ventricle to the left atrium at A_2 of $< 50\%$ of the peak gradient also identified patients who needed valve operation (sensitivity 75% and specificity 68%).

These findings may help to identify patients who require operation. They suggest that there are significant differences in the dynamics of flow velocities in patients with mitral regurgitation, possibly related to the relative resistances to retrograde and anterograde flow.

The severity of mitral regurgitation is an important factor in determining the need for valve operation. There are technical limitations with all current methods of quantification including contrast ventriculography, which has generally been regarded as the reference standard.¹⁻⁴ Doppler echocardiography, though widely used to detect mitral regurgitation,⁵ is less well established as a method of determining its severity. Pulsed Doppler has been used to map the extent of regurgitation into the left atrium.^{6,7} This procedure is time consuming and may be misleading, particularly when an eccentric jet caused by mitral valve prolapse extends far back into the left atrium without severe regurgitation. Similarly, determination of regurgitant fraction with pulsed Doppler also has limitations because it is necessary to estimate the mitral valve area and flow profile or because there is additional valve regurgitation at the aortic or tricuspid valve.^{8,9}

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The present study arose out of an examination of the relation between events documented by M mode and continuous wave Doppler tracings of patients with mitral regurgitation. Particular attention was paid to the duration of mitral regurgitant flow after end ejection and to the contour of the terminal portion of the Doppler profile. The aim was to identify time intervals that might distinguish patients who required valve operation from those who did not.

Patients and methods

PATIENTS

All patients with mitral regurgitation referred for Doppler echocardiography between January 1986 and January 1987 were studied retrospectively. We excluded patients with other important valve disease. We did not need to exclude any patients because we were unable to obtain Doppler echocardiographic measurements. The standard of comparison that we used was that of "outcome", namely whether or not

mitral valve operation was advised. The clinical criteria for valve operation included: (a) limitation of exercise tolerance; (b) physical signs compatible with severe mitral regurgitation, including a third heart sound; (c) radiological evidence of cardiac enlargement and pulmonary congestion; (d) echocardiographic evidence of increased left ventricular cavity size and stroke volume along with anatomical abnormalities of the mitral valve.

The 64 patients studied belonged to three groups. Group 1 comprised those patients with severe mitral regurgitation and who required operation. Group 2 consisted of patients with mitral regurgitation secondary to severe left ventricular disease, and group 3 consisted of patients with mild or moderate primary mitral regurgitation in whom operation was not advised. There were 20 patients (11 men, nine women, mean (SD) age 60 (17)) in group 1. The cause of mitral regurgitation was flail chordae tendineae in nine (45%), mitral valve prolapse in six (30%), rheumatic disease in two (10%), papillary muscle infarction in two (10%), and endocarditis in one (5%). Mitral valve repair was performed in 10 and mitral valve replacement in eight. Two patients are awaiting operation. In all cases the findings at operation were those of severe mitral regurgitation. Group 2 comprised 22 patients (16 men, six women, mean (SD) age 64 (14.8)). Eleven had ischaemic left ventricular disease with papillary muscle dysfunction and 11 had dilated cardiomyopathy. The remaining 22 patients (18 men, four women, mean age 60 (17)) comprised group 3. Ten (45%) had mitral valve prolapse and three of these developed endocarditis; four (18%) had papillary muscle dysfunction; three (14%) had rheumatic mitral regurgitation; one (4.5%) had flail chordae tendineae; one (4.5%) had annular calcification, and there was no clear cause in three (14%).

ECHOCARDIOGRAPHY

M mode and cross sectional echocardiograms were obtained with an Advanced Technical Laboratory 860 C Imager equipped with a 3.5 MHz mechanical transducer. M mode echocardiograms were recorded on a Honeywell (Echoline 22) strip chart recorder at a paper speed of 100 mm/second. The system was linked to a Doptek Spectrascan, and continuous wave Doppler signals were similarly recorded at 100 mm/second paper speed, with a 2.0 MHz transducer, at a range of frequency shift of 16 kHz. Recordings were made from the apex with the patient in the left lateral decubitus position. The delay in Doppler signal because of spectral analysis was <5 ms. A phonocardiogram at the second right interspace and an electrocardiogram were recorded simultaneously with

both M mode and Doppler recordings (figs 1 and 2). We used calipers to measure the following, as the mean value of three beats in patients in sinus rhythm and 5–10 beats in those in atrial fibrillation:

- (a) R R interval and heart rate.
 - (b) End diastolic and end systolic dimensions measured synchronously with onset of Q wave and A_2 , respectively. Fractional shortening was derived as systolic reduction in dimension divided by end diastolic dimension.
 - (c) Left ventricular filling time—the interval between initial separation and final closure of the mitral leaflets at the beginning and end of diastole.
 - (d) Q– A_2 interval (electromechanical systole), taken from the onset of the Q wave to the first high frequency deflection on the phonocardiogram. The identity of A_2 was checked by confirming that it was synchronous with aortic closure on the aortic echogram.
 - (e) Isovolumic relaxation time, the interval A_2 to mitral valve opening. Records were obtained at the level of the tips of the mitral leaflets to display initial cusp separation.
 - (f) Interval A_2 to the end of mitral systolic flow.
 - (g) Relative gradient at A_2 , measured as the left ventricular to left atrial pressure difference at A_2 , expressed as a percentage of the peak left ventricular to left atrial pressure difference.
 - (h) Duration of retrograde mitral systolic flow measured from the continuous wave Doppler trace.
- Interobserver variability was small (<10 ms). Beat to beat changes in end-systolic and early diastolic time intervals in patients with atrial fibrillation were also small, and within the 10 ms interval to which all measurements were rounded off.

ANGIOGRAPHIC EXAMINATION

Angiography was only performed in patients in whom there was doubt about the severity of mitral regurgitation after clinical assessment and non-invasive examination, or when concomitant coronary artery disease was suspected. In these patients right heart catheterisation was performed in addition to left ventricular cineangiography in the 30° right anterior oblique projection. The angiographic severity of mitral regurgitation was classified as follows: 1+, contrast cleared the left atrium with each cardiac cycle; 2+, contrast partially cleared the left atrium with each cardiac cycle; 3+, contrast progressively opacified the left atrium so that it equalled the opacification of the left ventricle and 4+, contrast rapidly opacified the left atrium within 1 to 2 cycles and opacification became greater than in the left ventricle and extended to the pulmonary veins.

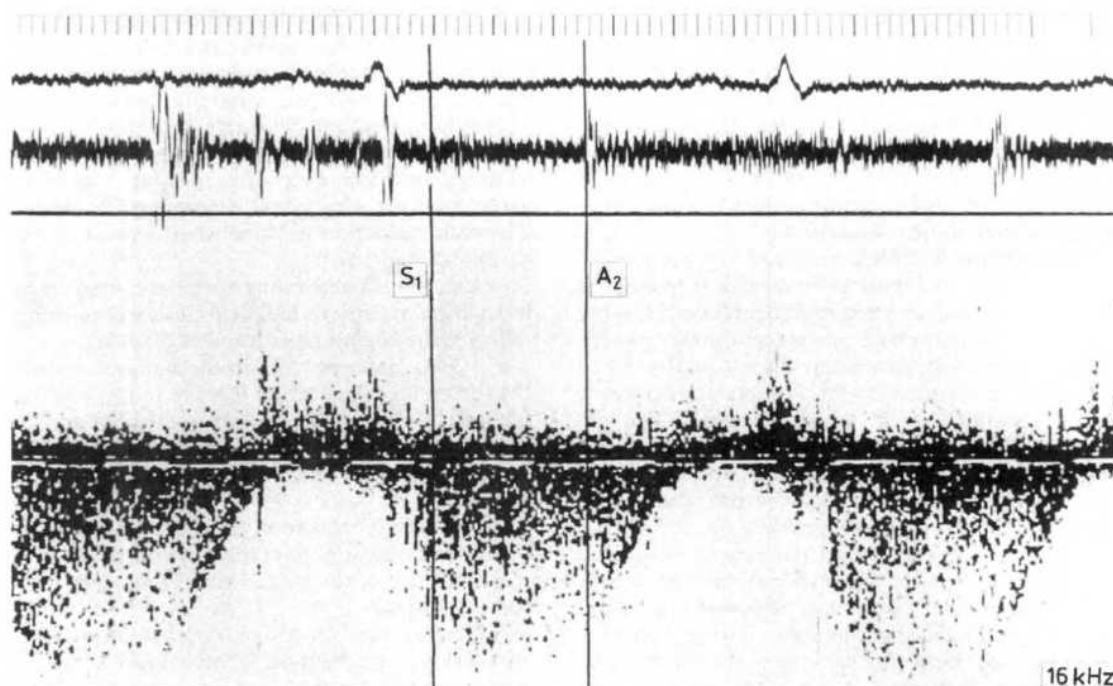


Fig 1 Continuous wave Doppler cardiogram from a patient with functional mitral regurgitation (recorded with simultaneous phonocardiogram). Mitral flow continued for 140 ms after A_2 , the aortic component of the second heart sound. S_1 , first heart sound. Full scale deflection = 16 kHz frequency shift, equivalent to a velocity of 6.4 m/s.

STATISTICAL ANALYSIS

The mean (1SD) was calculated for each measurement in each group and compared by the paired t test.

Results

Table 1 summarises the clinical features. There was no significant difference between the three groups in age or heart rate, or between groups 1 and 2 in clinical or radiological manifestations of clinical severity or pulmonary congestion. Table 2 shows the echocardiographic estimates of left ventricular function. These reflected the expected differences between the groups. There was no significant difference between groups 1 and 3 for end systolic and end diastolic cavity size, though fractional shortening was significantly increased in group 1 ($p < 0.05$). There was no significant difference between any of the groups in isovolumic relaxation time; this was significantly shorter than normal (60 (10) ms) in all three. The values for groups 1 to 3 were 20 (25) ms, 30 (30) ms, and 30 (40) ms (all $p < 0.001$ compared with the normal value). The mean interval from A_2 to end of mitral retrograde flow was significantly shorter in

group 1 than in group 2 ($p < 0.001$) or group 3 ($p < 0.001$). The mean of group 2 was significantly less than that of group 3 ($p < 0.05$). In all patients with mitral regurgitation severe enough to require operation, this interval was < 55 ms; the mean value in group 1 was 40 (15) ms compared with 90 (35) ms in group 2, and 75 (20) ms in group 3. The sensitivity, specificity, and predictive accuracy of an interval ≤ 55 ms in predicting the need for valve operation was 100%, 86%, and 91%, respectively. There were three false positives in group 3, in whom the intervals from A_2 to cessation of mitral flow were 45, 45, and 53 ms. The first patient has angiographic grade 4+ mitral regurgitation but is only mildly limited, and is being observed for symptomatic deterioration before operation is recommended. The other two had moderately impaired left ventricular function with clinically mild to moderate mitral regurgitation and have not been catheterised. There were three false positives in group 2 but all had dilated cardiomyopathy with severely reduced fractional shortening (9%, 14%, and 14%). They did not appear to have severe mitral regurgitation clinically and could be readily distinguished from group 1.

The relative gradient at A_2 was also significantly

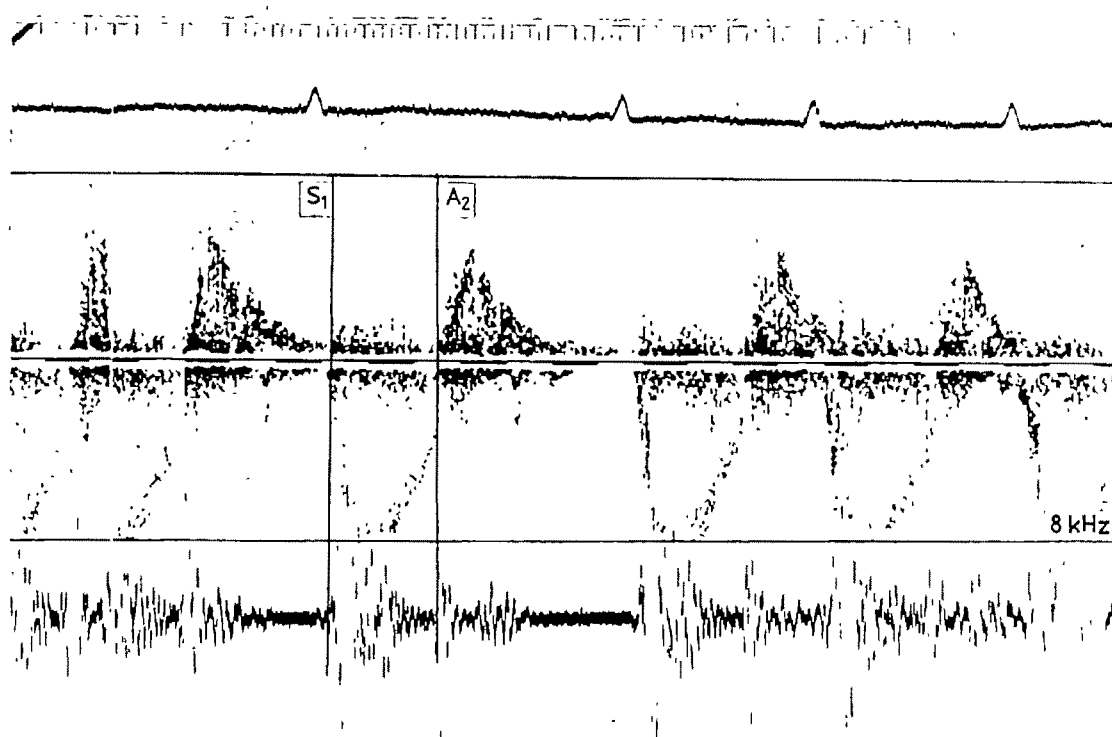


Fig 2 Continuous wave Doppler cardiogram from a patient with severe mitral regurgitation caused by ruptured posterior chorda tendineae. The end of mitral regurgitant flow was synchronous with A_2 . Full scale deflection = 8 kHz, equivalent to a velocity of 3.2 m/s. Note also cessation of regurgitant murmur in mid-systole.

lower in group 1 (35 (15%)) than in group 2 (55 (20%)) ($p < 0.005$) and group 3 (60 (20%)) ($p < 0.001$). A ratio of $< 50\%$ identified those who required valve operation, with a sensitivity of 75% and a specificity of 68%. The correlation between isovolumic relaxation time and the interval from A_2 to end of mitral retrograde flow was weak, with correlation coefficients of 0.24, 0.45, and 0.58, respectively. That between A_2 to cessation of flow (x) and relative gradient at A_2 (y) was 0.57, with a regression equation of $y = 0.37x + 24$, and the standard error of the estimate 16%. When a combination of A_2 to cessation of flow of $< 55\%$ and a relative gradient at A_2 of $< 50\%$ was used, the specificity rose to 90% and the sensitivity remained at 100%. Table 3 summarises the mean values for the systolic time intervals and left ventricular filling time. The Q- A_2 interval was significantly shorter in group 1 but this was of no predictive accuracy in individual patients.

Left ventricular angiography was performed in eight (40%) out of 20 group 1 patients, seven had 4+ mitral regurgitation. The remaining patient was considered to have 3+ mitral regurgitation and after several months of symptomatic deterioration had

mitral valve repair without recatheterisation. Three group 2 patients underwent ventriculography and were shown to have 1+, 2+, and no mitral regurgitation. In group 3, five patients were studied angiographically; there was 2+ mitral regurgitation in two, 3+ in two, and 4+ in the patient awaiting operation. Thus in the limited number of patients studied, the correlation between angiographic and Doppler assessment of mitral regurgitation was close.

Discussion

It is difficult to compare different methods of measuring mitral regurgitation because there is no reference standard.^{10,11} Volume measurements such as cardiac output, left ventricular volume, ejection fraction, or regurgitation fraction and pressure measurements including pulmonary arterial and wedge pressures, all provide ancillary information but seem to be intrinsically limited as indicators of the appropriate timing of mitral valve operation. In addition to technical limitations, this may be partly because of difficulties in identifying additional complications caused by left ventricular disease. For

Table 1 Clinical details (number (%)) of study groups

Variables	Group 1	Group 2	Group 3
Symptoms:			
NYHA I/II	4 (20)	4 (18)	17 (77)
NYHA III/IV	16 (80)	18 (82)	5 (23)
Cardiomegaly on chest x ray:			
Present	17 (85)	22 (100)	9 (41)
Absent	3 (15)	0	13 (59)
Clinical pulmonary congestion:			
Present	17 (85)	18 (82)	5 (23)
Absent	3 (15)	4 (18)	17 (77)
Radiographic pulmonary congestion:			
Present	17 (85)	17 (77)	9 (41)
Absent	3 (15)	4 (18)*	13 (59)
Rhythm:			
Sinus rhythm	13 (65)	15 (68)	17 (77)
Atrial fibrillation	7 (35)	7 (32)	3 (14)
Paced			2 (9)

*One value missing.

NYHA, New York Heart Association

example, patients with a reduced stroke volume into a non-compliant left ventricle may require mitral valve operation just as much as those with a larger stroke volume into a compliant one. In view of the highly subjective component of grading angiographic mitral regurgitation,³ routine cardiac catheterisation and ventriculography was not performed on all of our patients. In many the diagnosis and haemodynamic severity of the mitral regurgitation was readily apparent by clinical and non-invasive assessment. Invasive investigations were only performed if there was some doubt about the severity of the lesion or because of the possibility of coexistent coronary artery disease, an approach that has been previously validated in a large series of patients.¹² In all operated patients the surgical findings confirmed severe mitral regurgitation. Since the aim of investigation is to determine clinical management, we concluded that

outcome based on assessment of all clinical data should be used as the reference standard rather than the result of any single test. Because this was a retrospective study its results did not influence the treatment of individual patients.

Our observations of the timing of regurgitant flow in patients with severe left ventricular disease confirm those of a previous small series.¹³ It is not possible, however, to extrapolate results from this limited population to patients with primary mitral regurgitation that requires operation. Indeed, there was a strong relation between the dynamics of retrograde flow and the severity of the regurgitation. The interval between A_2 and the end of flow was consistently shorter in patients who were shown to need operation. In particular, a reduction in the interval from aortic valve closure to the end of retrograde flow to <55 ms consistently identified such patients with no false negatives. There were six false positives, one of whom may well require operation in the future, while the remainder could be readily distinguished on other grounds.

A more abrupt deceleration pattern was associated with an early end to the Doppler signal. This was reflected in the transmitral gradient at the time of aortic valve closure, which was a less accurate predictor than the interval from A_2 to cessation of flow when used alone but in combination with other measurements seemed to provide additional information. The velocity profile in the non-surgical group seemed to reach a peak in mid-ejection, but with severe regurgitation, there was an earlier peak that was more reminiscent of a normal aortic velocity profile (fig 2). The two profiles were easily distinguished because blood flow velocities caused by mitral regurgitation, whatever their profile, are much higher than those of aortic flow if there is no aortic stenosis. To measure these time intervals A_2 must be unequivocally identified, especially in patients with

Table 2 Left ventricular cavity size (mean (SD)) in study groups

Measurement	Group 1	Group 2	Group 3	1 v 2	1 v 3	2 v 3
End systolic dimension (mm)	35 (10)	55 (10)	40 (10)	$p < 0.001$	NS	$p < 0.001$
End diastolic dimension (mm)	60 (10)	65 (10)	60 (10)	NS	NS	NS
Fractional shortening (%)	40 (10)	15 (5)	35 (10)	$p < 0.001$	$p < 0.05$	$p < 0.001$

Table 3 Left ventricular function (mean (SD)) in the study groups

Interval	Group 1	Group 2	Group 3	1 v 2	1 v 3	2 v 3
RR interval (ms)	670 (170)	680 (130)	730 (160)	NS	NS	NS
A_2 to cessation of flow (ms)	40 (15)	90 (35)	75 (20)	$p < 0.001$	$p < 0.001$	$p < 0.001$
Relative gradient at A_2 (%)	35 (15)	55 (20)	60 (20)	$p < 0.005$	$p < 0.001$	NS
Isovolumic relaxation time (ms)	20 (25)	30 (30)	30 (40)	NS	NS	NS
Q- A_2 interval (ms)	330 (30)	360 (50)	365 (45)	$p < 0.001$	$p < 0.001$	$p < 0.001$
Left ventricular filling time (ms)	330 (95)	400 (85)	400 (95)	$p < 0.05$	$p < 0.05$	NS
Duration of systolic mitral flow (ms)	300 (95)	380 (60)	340 (84)	$p < 0.001$	NS	NS

left bundle branch block or paced rhythm in whom an error might be caused by a delay in A_2 . Conversely, A_2 itself may occur early and be soft when mitral regurgitation is severe. The timing of aortic valve closure must therefore be routinely confirmed from a concomitant aortic echogram.

The advantages of the present technique were its ease and relative simplicity. We found no patient in whom the interval A_2 to cessation of retrograde flow could not be measured and only one in whom it was impossible to obtain the relative gradient at A_2 . The method is equally applicable to patients with atrial fibrillation. In addition, it was unnecessary to measure the areas of the aortic or mitral orifices, as is required for Doppler determination of regurgitant fraction. Incomplete opening of the aortic valve followed by premature closure, seen in several of our patients may well prevent reliable estimates of aortic flow from velocity determinations. Derivation of mitral orifice area requires computer linked planimetry and is influenced by limited lateral resolution of echocardiographic equipment used for cross sectional imaging and the pattern of leaflet movement. Not surprisingly, Doppler assessment often shows "regurgitant fractions" of 20% in normal valves.⁸ Although the degree of mitral regurgitation can be estimated by mapping the regurgitant flow in the left atrium, this can be significantly overestimated or underestimated. The method is very time consuming when simple pulsed Doppler is used. Colour flow mapping speeds up the investigation; however, with this technique small alterations in transducer angulation and subtle gain setting modifications also lead to uncertainties.¹⁴ The present method is based on relative velocities and time intervals and so is not sensitive to transducer angulation.

In contrast to the consistent relation between the need for valve operation and the length of the interval from A_2 to cessation of mitral retrograde flow, we found no correlation between the clinical or radiological evidence of pulmonary congestion and the isovolumic relaxation period. This might seem to be paradoxical, because the height of the left atrial "v" wave is related to the severity of regurgitation and raised left atrial pressure is associated with a short isovolumic relaxation time both in left ventricular disease¹⁵ and mitral regurgitation. The interval A_2 to cessation of retrograde mitral flow was short only in group 1 patients and this must therefore reflect some other aspect of the disordered physiology of mitral regurgitation. When regurgitation is severe, functional end systolic volume seems to be achieved earlier. This suggestion was supported in the present study by the $Q-A_2$ interval being significantly shorter in group 1 than either groups 2 or 3, with several patients showing early partial aortic

closure even before A_2 . The similarity between the aortic and mitral velocity profiles, both in form and timing, in patients with severe mitral regurgitation suggests that a major determinant of retrograde flow is the overall resistance to regurgitation and its relation with that to forward flow. Conditions thus seem similar to those governing ejection in patients with a large ventricular septal defect, where flows are neither determined nor predicted by pressures in the two great arteries, but depend more closely on the relative resistances.

We conclude that analysis of flow dynamics may be helpful not only in determining severity in individual cases, when used in conjunction with clinical features, but also seem to provide some insight into the pathophysiology of the regurgitation itself. Electromechanical systole and flow rate must be in balance. In severe mitral regurgitation this relation is likely to be severely disturbed, with low resistance to ejection being accompanied by a very rapid fall in left ventricular volume. Thus it seems that aspects of mitral regurgitation other than regurgitant fraction and pressure equalisation should be investigated when such patients are being assessed for operation. The idea of relative left atrial and aortic resistance as a determinant of flow may thus provide insight into the physiological disturbances determining flow and so improve the management of patients with severe mitral regurgitation.

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Comparison of the haemodynamic effects of epoprostenol (prostacyclin) and tolazoline

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SUMMARY The haemodynamic effects of infusion of epoprostenol (prostacyclin) and bolus injection of tolazoline were compared in a crossover study in 11 children with pulmonary hypertension caused by pulmonary vascular disease. The children were studied during cardiac catheterisation, while they were anaesthetised, paralysed, and ventilated with 100% oxygen. The order of drug administration was not randomised because tolazoline has a half life of hours whereas epoprostenol has a half life of a few minutes. Both drugs caused pulmonary and systemic vasodilatation, and there were no significant differences between the two. The 95% confidence intervals suggest that tolazoline did not have a clinically important haemodynamic advantage over epoprostenol. Previous reports suggest that serious side effects are common when tolazoline is used in repeated doses; epoprostenol has only a few minor side effects that are rapidly reversible when the infusion is stopped.

Epoprostenol is more expensive than tolazoline but this study suggests that epoprostenol is a more suitable pulmonary vasodilator if more than a single dose is required.

Tolazoline is an α adrenergic antagonist and H_2 agonist agent that has been widely used in infants and children for the preoperative assessment of congenital heart disease,¹ the management of postoperative pulmonary hypertensive crises,² and pulmonary hypertension caused by pulmonary parenchymal disorders.³ It is not an ideal agent, however, because of the prevalence and severity of side effects, and its prolonged duration of action. Depending on the dose used, 30%–80% of infants treated with tolazoline infusion have side effects, which may contribute to mortality.^{4–6} These include hypotension,⁷ thrombocytopenia, pulmonary and gastrointestinal haemorrhage, seizures, oliguria and renal failure severe enough to necessitate peritoneal dialysis,^{8,9} haematuria, hyponatraemia, abdominal distension, and duodenal perforation.^{4,5,10} The half life of the drug ranges from 90 minutes to more than 40 hours and is inversely proportional to the urine flow rate.¹¹

We have previously shown that epoprostenol (prostacyclin) is a pulmonary vasodilator in children with congenital heart disease¹² and bronchopulmonary dysplasia.¹³ It has a half life of minutes and few

side effects. These are rapidly reversible when the infusion is stopped.¹⁴ These features may make epoprostenol a safer agent than tolazoline. We therefore carried out a study to compare the haemodynamic effects of these two drugs.

Patients and methods

PATIENTS

Table 1 shows the details of the 11 children studied. All had raised pulmonary vascular resistance (>3 mm Hg. l^{-1} . $min.$ m^2) during ventilation with 100% oxygen. In nine patients this increase was primarily the result of congenital heart disease, and in two the main diagnosis was bronchopulmonary dysplasia. The response of the pulmonary circulation to vasodilators was studied as part of the preoperative or prognostic assessment of pulmonary vascular disease or to optimise vasodilator treatment used in the management of pulmonary hypertensive crises. No child had a ductus arteriosus at the time of study. Children 2 and 8 had undergone palliative Mustard operations before the study. Informed consent was obtained from the parents of all the patients before the procedure, and the protocol was approved by the Brompton Hospital ethics committee.

METHODS

Full details of the measurement techniques have

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Table 1 Details of patients studied, given in descending order of baseline pulmonary vascular resistance (PVR)

Case No	Age (yr)	Diagnosis	PVR (mm Hg.l ⁻¹ .min.m ²)		Qp (l.min ⁻¹ .m ²)		PAP (mm Hg)	
			Baseline	Best	Baseline	Best	Baseline	Best
1	1	EFE	25.00	14.10	2.95	3.55	88	59
2	7	TGA, VSD	16.79	16.39	3.46	3.91	63	63
3	3	DA, BPD	14.87	7.00	4.07	5.47	74	50
4	2	VSD, PAB, CA	11.10	7.20	4.10	4.40	54	38
5	10/12	DA, BPD	8.30	7.35	2.95	3.60	30	30
6	9/12	AVSD, DS	8.20	5.90	5.30	6.70	52	48
7	4	DA, VSD, PMV	6.08	4.46	4.85	5.00	55	44
8	3	TGA, PAB	5.30	5.10	2.90	3.60	24	24
9	4	DORV, DA	3.87	3.54	9.68	9.68	40	31
10	6	VSD, DA, CA	3.80	3.40	4.40	4.40	27	23
11	12	VSD	3.70	3.20	4.12	7.64	23	23

AVSD, atrioventricular septal defect; BPD, bronchopulmonary dysplasia; CA, coarctation; DA, ductus arteriosus; DORV, double outlet right ventricle; DS, Down's syndrome; EFE, endocardial fibroelastosis; PAB, pulmonary artery banded; PAP, pulmonary artery pressure; PMV, parachute mitral valve; Qp, pulmonary blood flow; TGA, transposition of the great arteries; VSD, ventricular septal defect.

been reported elsewhere.^{15,16} In summary, the children were anaesthetised with intravenous etomidate throughout the study. They were paralysed and ventilated via a close-fitting endotracheal tube. The stability and adequacy of ventilation throughout the study were monitored by mass spectrometry of end tidal gases. The children were initially ventilated with air. Fluid filled catheters were introduced percutaneously into the femoral artery and vein and positioned in the aorta and pulmonary artery respectively. Any necessary diagnostic procedures, including measurement of left and right atrial pressures but excluding angiography, were performed before the measurements were made.

When a respiratory steady state had been reached (that is an end tidal P_{CO_2} stable to within 0.25 kPa over several minutes)¹⁶ we measured aortic and pulmonary artery pressure and pulmonary and (where possible) systemic blood flow. We measured flow by the direct Fick principle. Oxygen consump-

tion was measured by remote respiratory mass spectrometry,^{15,16} and blood oxygen content was calculated by the subroutine of Kelman.¹⁷ The respiratory exchange ratio was measured on air and was used in the equation to calculate oxygen consumption on 100% oxygen.¹⁶

After the measurements on air, the children were ventilated with 100% oxygen. Ventilation and adequacy of nitrogen washout on air and oxygen were compared by monitoring the expired gases. After 10 minutes on 100% oxygen, when nitrogen washout was always complete, all measurements were repeated. The patients breathed 100% oxygen for the rest of the study.

After the measurements on 100% oxygen alone were completed (baseline 1), the vasodilators were administered. Figure 1 summarises the protocol. Because of the differences in half life, we always had to administer epoprostenol before tolazoline. We gave epoprostenol by continuous intravenous

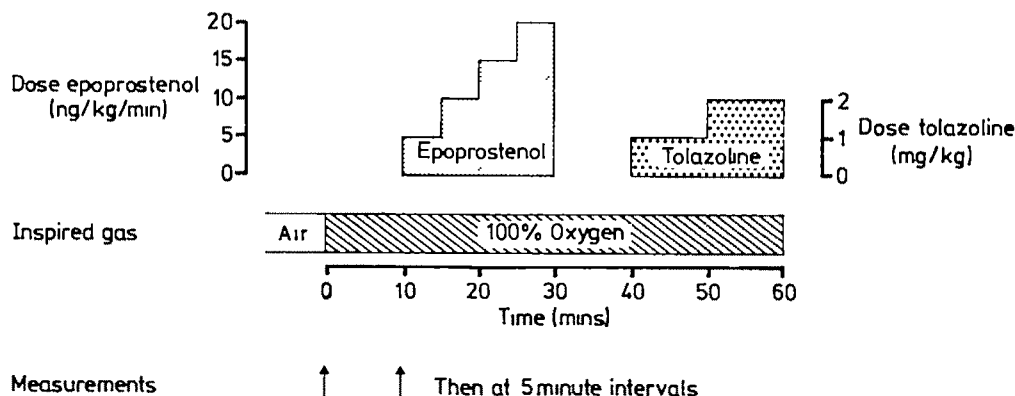


Fig 1 The study protocol. Measurements were made while the patient breathed air, after breathing 100% oxygen for ten minutes, and every five minutes thereafter. Epoprostenol was given by continuous intravenous infusion and tolazoline by bolus injection into the pulmonary artery.

infusion into a peripheral vein and started with a dose of 5 ng/kg/min. This was increased by increments of 5 ng/kg/min until a dose of 20 ng/kg/min was reached. Measurements were made after five minutes at each dose level. We would have stopped the infusion if mean aortic pressure had fallen by more than 20 mm Hg, but this was never necessary. When the final epoprostenol measurements were complete the infusion was stopped. The measurements were then made five and ten minutes after the drug had been stopped. The results at 10 minutes were regarded as baseline 2. Then we gave tolazoline 1 mg/kg as a bolus injection via the pulmonary artery catheter. The measurements were repeated five and ten minutes after the bolus ($n = 11$). Provided mean aortic pressure had not fallen by more than 20 mm Hg, a further 1 mg/kg of tolazoline was then given and the final measurements were made five and ten minutes after this second bolus ($n = 8$). In two patients the second dose was not given because of hypotension, and in the third it was not given because the endotracheal tube was becoming blocked with secretions and the necessary endotracheal toilet disrupted the respiratory steady state.

STATISTICAL ANALYSIS

Table 1 shows that there were big differences in the initial pulmonary haemodynamic function in the patients studied. This variability was removed by subtracting the initial measurement made on 100% oxygen alone from all subsequent measurements, so that analysis was restricted to the change in the variables. These data were inspected and found to be normally distributed. The mean and the 95% confidence intervals were calculated for each set of measurements.

It is possible to compare the tolazoline results either with the first baseline on 100% oxygen, before any drugs were given (B1 in the figures), or with the second baseline, 10 minutes after epoprostenol and just before tolazoline was given (B2b in the figures). We also had to decide whether to analyse the 11 sets of data that included measurements of the effects of only the first dose of tolazoline or the eight complete sets of data that included both doses of tolazoline. We decided to perform all four combinations of analyses to see whether the choice of numbers or baseline materially affected the conclusions. Thus the comparisons for pulmonary vascular resistance, pulmonary blood flow, pulmonary artery pressure, heart rate, and aortic pressure were (first baseline minus maximal epoprostenol effect) versus (first baseline minus maximal tolazoline effect) for $n = 11$ and $n = 8$; and (first baseline minus maximal epoprostenol effect) versus (second baseline minus maximal tolazoline effect) for $n = 11$ and $n = 8$. Differences

between drug effects were also normally distributed and were also expressed as mean and 95% confidence intervals of the difference.

The comparisons for systemic blood flow, systemic vascular resistance, and the ratio of pulmonary and systemic vascular resistances are based on only six sets of data because systemic blood flow can only be measured accurately by the Fick principle if a truly mixed venous blood sample can be obtained.¹⁸ This is not possible if there is left to right shunting. Only four of these six patients were given the second dose of tolazoline. Data for the second dose were not analysed because the numbers are so small. For these variables, the comparisons were (first baseline minus maximal epoprostenol effect) versus (first baseline minus maximal tolazoline effect) ($n = 6$); and (first baseline minus maximal epoprostenol effect) versus (second baseline minus maximal tolazoline effect) ($n = 6$). The data for individuals were inspected to see how many patients had the greatest change in pulmonary vascular resistance, aortic pressure, and heart rate on epoprostenol and how many on tolazoline. The significance of these differences was assessed by a test of proportions.

Results

Figures 2 to 9 show the mean and 95% confidence intervals for the changes in pulmonary vascular

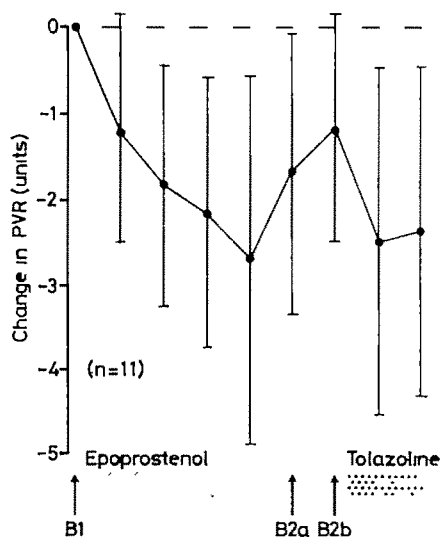


Fig 2 Change (mean, 95% CI) in pulmonary vascular resistance (PVR) with epoprostenol and tolazoline. In this and figs 3 to 9, B1 is the baseline measurement on 100% oxygen before any drugs were given and B2a and B2b the baselines respectively five and ten minutes after stopping the infusion of epoprostenol.

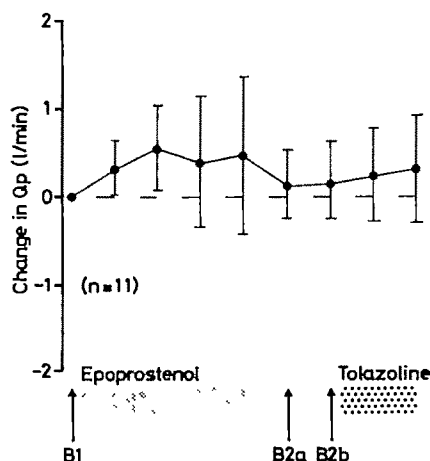


Fig 3 Change (mean, 95% CI) in pulmonary blood flow (Q_p) with epoprostenol and tolazoline infusions.

resistance, pulmonary blood flow, pulmonary artery pressure, heart rate, aortic pressure, systemic vascular resistance, systemic blood flow, and the ratio of pulmonary to systemic vascular resistances. The results for the second dose of tolazoline are not plotted because they are incomplete. In summary, there were significant falls in pulmonary vascular resistance on both drugs (fig 2), a significant rise in heart rate with tolazoline and a trend to rise with epoprostenol (fig 5), and significant falls in systemic vascular resistance with both drugs (fig 8). Neither drug caused a significant change in the ratio of pulmonary to systemic vascular resistance (fig 9).

Tables 2 and 3 show the mean and the confidence intervals of the differences between the drugs, analysed as described above. If epoprostenol caused a

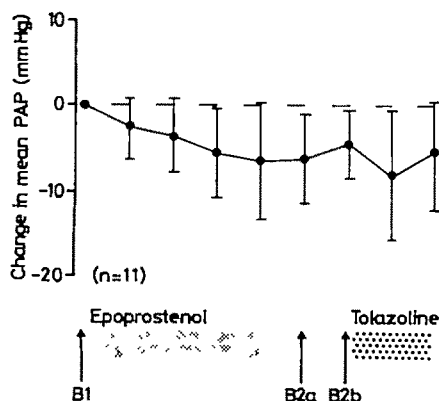


Fig 4 Change (mean, 95% CI) in mean pulmonary artery pressure (PAP) with epoprostenol and tolazoline infusions.

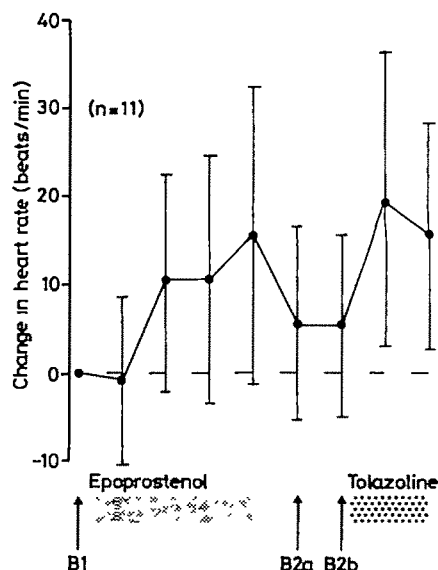


Fig 5 Change (mean, 95% CI) in heart rate with epoprostenol and tolazoline infusions.

greater change than tolazoline the change was given a positive value; if tolazoline caused a greater change than epoprostenol the change was given a negative value. The method of analysis did not materially alter the conclusions, which are summarised below. The results in the tables were combined by selecting the biggest positive and negative value for each drug for each physiological measurement—that is, the most extreme values for each drug for each row in the tables irrespective of the method of analysis. This

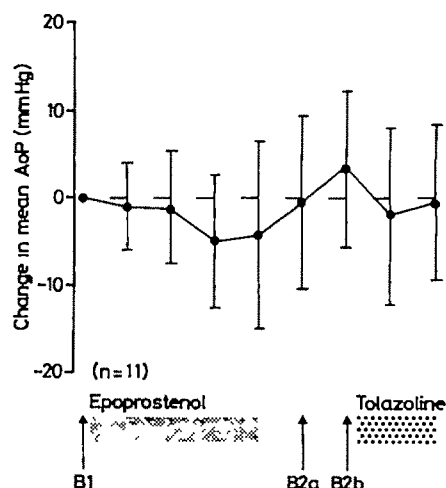


Fig 6 Change (mean, 95% CI) in mean aortic pressure (AoP) with epoprostenol and tolazoline infusions.

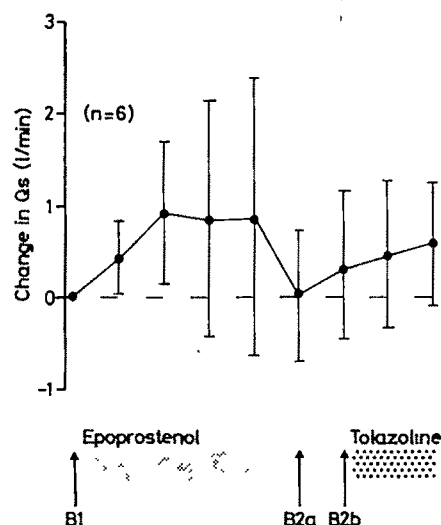


Fig 7 Change (mean, 95% CI) in mean systemic blood flow (Q_s) with epoprostenol and tolazoline infusions.

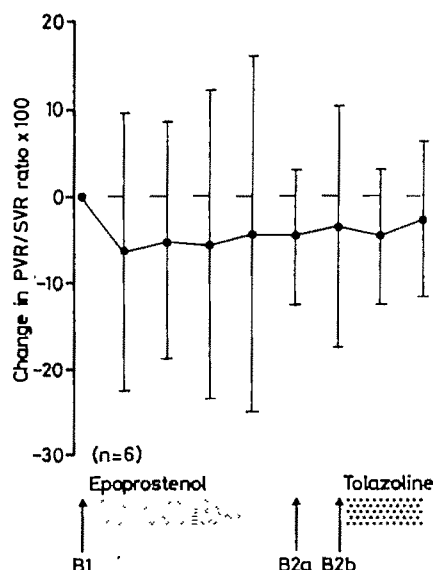


Fig 9 Change (mean, 95% CI) in the ratio of pulmonary to systemic vascular resistance $\times 100$ (PVR/SVR ratio) with epoprostenol and tolazoline infusions.

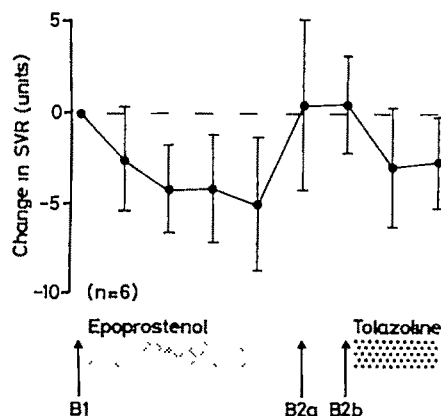


Fig 8 Change (mean, 95% CI) in systemic vascular resistance (SVR) with epoprostenol and tolazoline infusions.

range of values is 95% certain to include the true value. The confidence intervals would have been narrower if only one column had been selected from the tables and the others had been excluded. The biggest positive value was the "best case" for epoprostenol and the biggest negative value was the "best case" for tolazoline. The direction of the effects (increase or decrease over baseline) is shown in figs 2 to 9.

On this basis, the confidence intervals for the differences between the drug effects on pulmonary vascular resistance are 4.01 to -0.74 units, for pulmonary blood flow 2.08 to -0.22 l/min, and for mean pulmonary artery pressure 12.5 to -4.8 mm Hg. The heart rate intervals are 11.3 to -18.7 beats/min. For the systemic circulation, the con-

Table 2 Mean and 95% confidence intervals for the changes in pulmonary vascular resistance (units, PVR), pulmonary blood flow (l/min, Q_p), pulmonary artery pressure (mm Hg, PAP), heart rate (beats/min, HR), and aortic pressure (mm Hg, AoP). (A minus sign means that the magnitude of the change was greatest with tolazoline)

	Baseline 1		Baseline 2	
	n = 11	n = 8	n = 11	n = 8
PVR	0.22 (0.88 to -0.44)	0.20 (1.14 to -0.74)	1.39 (3.16 to -0.38)	1.75 (4.01 to -0.51)
Q_p	0.53 (1.15 to -0.09)	0.66 (1.54 to -0.22)	0.71 (1.53 to -0.11)	0.98 (2.08 to -0.12)
PAP	-0.2 (4.4 to -4.8)	0.3 (4.7 to -4.1)	4.4 (10.5 to -1.7)	5.3 (12.5 to -1.9)
HR	-3.5 (0.9 to -7.9)	-9.6 (-0.5 to -18.7)	1.8 (11.3 to -7.7)	-1.8 (7.8 to -11.4)
AoP	6.5 (15.0 to -2.0)	7.0 (15.3 to -1.3)	3.2 (12.5 to -6.1)	6.6 (16.2 to -3.0)

Baseline 1, tolazoline effects compared with baseline before any drugs given (B1 in figures); baseline 2, tolazoline effects compared with second baseline 10 minutes after epoprostenol was stopped and before tolazoline was given (B2b in figures). n = 11, 11 sets of data analysed; these included only the first dose of tolazoline; n = 8, analysis of the eight sets of data that included both doses of tolazoline.

Table 3 Mean and 95% confidence intervals for the changes in systemic blood flow (Q_s), systemic vascular resistance (SVR), and the ratio of pulmonary to systemic vascular resistance (PVR/SVR ratio)

	Baseline 1	Baseline 2
Q_s (l/min)	0.51 (1.37 to -0.35)	0.84 (2.39 to -0.71)
SVR (units)	2.53 (6.42 to -1.36)	2.07 (6.86 to -2.72)
PVR/SVR ratio	0.04 (0.19 to -0.11)	0.07 (0.12 to -0.02)

All comparisons were based on six patients, and the data for the second dose of tolazoline ($n = 4$ only) were discarded. Baseline 1 and baseline 2, see table 2

confidence intervals are 16.2 to -6.1 mm Hg for aortic pressure, 2.39 to -0.71 l/min for systemic blood flow, and 6.86 to -2.72 units for systemic vascular resistance. The confidence intervals for the change in ratio of pulmonary to systemic vascular resistance are 0.19 to -0.11.

The individual data were assessed separately. Epoprostenol caused the greater fall in pulmonary vascular resistance in 7/11 (8/11 if tolazoline is compared with the second baseline), a greater fall in aortic pressure in 8/11 (7/11, second baseline), and a greater rise in heart rate in 2/11 (9/11 second baseline).

Discussion

Before drawing any conclusions from the findings described above, the study design must be considered in detail. This discussion centres on the inevitable difficulties of this sort of comparison and the ways of interpreting the results.

The classic method of comparing these two agents would be to use two large matched groups of patients, and allocate at random one group to receive tolazoline and one to receive epoprostenol. This was rejected, because matching for age, cardiac diagnosis, baseline pulmonary vascular resistance, and reactivity for two groups of sufficient size would be impossible. We therefore decided to use a crossover design and give both drugs to all patients. Ideally, the order would have been randomised, but because tolazoline has a half life of many hours¹¹ and epoprostenol one of a few minutes,¹⁴ epoprostenol always had to be administered first. The resulting problems of order effects and possible interactions between the drugs are discussed below; we adopted this design as the best compromise between what was ethically possible and experimentally desirable. Also the inspired oxygen tension needed to be the same for both drugs. Because we wanted to detect the lowest pulmonary vascular resistance for each individual for clinical purposes, we decided to use 100% oxygen, which has been shown to be additive to the effects of both epoprostenol^{12,13} and tolazoline.¹⁹

The initial part of the study confirms previous results,^{12,13} and the interpretation is straightforward. Epoprostenol, when added to 100% oxygen, caused a further fall in pulmonary vascular resistance, with systemic hypotension and tachycardia. When the infusion was stopped, these variables reverted towards baseline. Ten minutes after stopping the infusion, mean pulmonary artery pressure was still a mean 4.5 mm Hg (95% confidence interval 8.4 to 0.6) below baseline. The other variables were not significantly different from baseline. Pulmonary vascular resistance was furthest from the baseline, largely owing to the results from three individuals in whom reversal was abnormally slow. When these three were omitted, the means $\pm$ 95% confidence intervals five and ten minutes after the end of the infusion were -0.33 (-0.87 to 0.21) and -0.13 (-0.9 to +0.64) units. We do not know why three patients should have apparently behaved differently; but in general, these results confirm that the half life of epoprostenol is short.¹⁴

The interpretation of subsequent measurements is less straightforward. It is possible that all the effects seen can be attributed solely to tolazoline. But some residual minor effects of epoprostenol may have interacted favourably or unfavourably with those of tolazoline. It is also possible that the prolonged anaesthesia, or exposure to hyperoxia, caused some of the changes we saw. The return of most of the measured variables nearly to the original baseline makes it unlikely that these are major factors. Nevertheless, because the drugs were always given in the same order, such effects cannot be excluded. Furthermore, although for the group the baseline measurements before and after the administration of epoprostenol were similar, there was individual variation, and perhaps it would be better to refer the tolazoline measurements to the original baseline or to the baseline attained just before it was given. Therefore, we analysed the tolazoline results by reference to each baseline in turn for the eight complete sets of data (both doses of tolazoline administered) and the eleven sets (the first dose of tolazoline). The mean differences and their confidence intervals are similar whichever analysis is chosen.

The results confirm that epoprostenol and tolazoline when added to 100% oxygen result in systemic and pulmonary vasodilatation and tachycardia.^{12,13,20} We were unable to detect significant differences between the haemodynamic effects of these two drugs. The confidence intervals can be used to assess the likelihood that a clinically significant difference was present but not detected. Tolazoline may have reduced the pulmonary vascular resistance by less than one unit more than

epoprostenol. Even if such a difference were genuine, it would be unlikely to be clinically important. Epoprostenol may have reduced pulmonary vascular resistance by up to 4 units more than tolazoline—a difference that would be clinically important. It is also possible, however, that epoprostenol causes more clinically significant systemic hypotension than tolazoline. One method of trying to assess the selectivity of an agent for the pulmonary circulation is to look at the ratios of pulmonary resistance to systemic vascular resistance. The mean and confidence intervals suggest that there is no real difference between the two agents, and that it is unlikely that such a difference was present but not detected.

The data for individual patients show that slightly more subjects had a greater reduction in pulmonary vascular resistance and aortic pressure with epoprostenol than with tolazoline; but these differences are also unlikely to be significant. It seems more likely that reactive pulmonary vessels will be dilated by any vasodilator agent. There is no reason to suppose that any particular class of drug is likely to be more effective for a substantial number of patients.

Some workers have reported increased haemodynamic benefit with doses of tolazoline of up to 10 mg/kg.^{4,11,21} If we had given higher doses to these children the conclusions might have been different. Side effects may be dose related, however, and at these high doses cause considerable toxicity. Two (18%) of our 11 patients had hypotension at a dose of 1 mg/kg of tolazoline and three (27%) out of eight had hypotension at a dose of 2 mg/kg. Administration of doses as high as 10 mg/kg cannot be regarded as standard practice.²²

We did not detect a major difference between the two drugs, and the confidence intervals suggest that tolazoline at doses of 1–2 mg/kg is unlikely to offer a clinically important, haemodynamic advantage over epoprostenol. It is possible but not confirmed that in the doses used epoprostenol is a more powerful pulmonary and systemic vasodilator than tolazoline. The choice between the two drugs can therefore be made on other grounds.

In this short term study, neither drug had serious side effects. Because a dose of 1 mg/kg of tolazoline caused hypotension in two patients we were unable to give a second bolus but no patient required treatment for hypotension. Repeated doses of tolazoline are often associated with severe side effects that may be a contributory cause of death. In addition, its long half life¹¹ means that any side effects can persist for many hours. By contrast, the side effects of epoprostenol are rapidly reversible when the infusion is stopped.¹⁴ The major side effect is hypotension, but others, such as headache and facial flushing,^{14,23} are unlikely to be important in patients who are being ventilated. The

main disadvantage of epoprostenol is its cost; a single vial costs more than £100 and 24 hours treatment more than £200, whereas treatment for the same period with tolazoline costs £10. It is safer to give epoprostenol; but for single doses for the preoperative assessment of congenital heart disease the risk of side effects is low enough to allow tolazoline to be used because it is cheaper. If more than a single dose is required, for example in the postoperative management of pulmonary hypertensive crisis, epoprostenol should probably be used first, and tolazoline used only if satisfactory results cannot be obtained with epoprostenol. Tolazoline reduced pulmonary vascular resistance more than epoprostenol in only three patients. Neither agent is likely to be suitable for outpatient treatment of children, for whom oral pulmonary vasodilators are more suitable. Long term domiciliary intravenous infusion of epoprostenol has, however, been used to treat adults with primary pulmonary hypertension.²⁴

We found that the haemodynamic effects of epoprostenol and tolazoline were similar in children with a high pulmonary vascular resistance complicating congenital heart disease. Earlier reports suggest that tolazoline has more severe side effects. Epoprostenol is more expensive; none the less we suggest that epoprostenol should replace tolazoline as a pulmonary vasodilator in these children, except possibly where only a single dose is needed.

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Acute haemodynamic effects of nifedipine in patients with ventricular septal defect

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SUMMARY The haemodynamic effects of nifedipine were studied in 14 patients (aged 8-14 years, seven male and seven female) with ventricular septal defect with and without pulmonary hypertension. All underwent left and right heart catheterisation. In each patient the pressures and heart rate were measured and blood samples were taken for oximetry before and after sublingual administration of 10 mg nifedipine.

In eight patients with ventricular septal defect without pulmonary hypertension (mean pulmonary artery pressure < 20 mm Hg) nifedipine significantly reduced the mean aortic pressure and systemic vascular resistance, and significantly increased heart rate. The other haemodynamic indices did not change significantly.

In six patients with ventricular septal defect complicated by pulmonary hypertension (mean pulmonary artery pressure > 20 mm Hg) nifedipine significantly increased systemic output, stroke volume, and heart rate, and significantly reduced systemic vascular resistance and the pulmonary to systemic flow ratio. The other haemodynamic indices did not change significantly.

Nifedipine had a beneficial effect in patients with ventricular septal defect complicated by pulmonary hypertension. It reduced the left to right shunt and increased the stroke volume. This effect was not seen in patients with ventricular septal defect uncomplicated by pulmonary hypertension.

Vasodilators are important and original agents for the treatment of congestive heart failure from various causes.¹⁻³ Their beneficial effects are more pronounced in the congestive heart failure secondary to valvar regurgitation⁴⁻⁶ and to mechanical complications of acute myocardial infarction.^{7,8} The reduction of peripheral vascular resistance has been followed by a substantial improvement of cardiac pump function, increased cardiac output, and attenuation of the clinical signs of venous and systemic congestion in these patients.^{1,5,6}

In animals with experimental ventricular septal defect vasodilators significantly reduced systemic vascular resistance, pulmonary to systemic flow ratio, and left to right shunt, and caused a considerable increase in the forward blood flow across the aorta.^{9,10} Opposite effects were seen with vasopressor drugs.¹¹ Clinical studies in patients with ventricular septal

defect and congestive heart failure confirmed these data.¹²⁻¹⁴

This study was designed to evaluate the acute haemodynamic effects of nifedipine in children with ventricular septal defect with and without pulmonary hypertension.

Patients and methods

We studied 14 children (seven male and seven female, aged 8-14 years) with isolated ventricular septal defect. Six patients were being treated for congestive heart failure—five with digitalis and diuretics and one with diuretics. In all of them treatment was stopped at least 24 hours before cardiac catheterisation. Informed consent was obtained from their parents. Right and left heart catheterisation was then performed in fasting patients after premedication with 1 mg/kg of intramuscular pethidine hydrochloride. Pressures were measured by fluid filled catheters connected to Bentley-Trantec Model 800 pressure transducers. The pressure signals and one electrocardiographic

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Table 1 Clinical data and treatment in patients with ventricular septal defects without pulmonary hypertension (group A) and with pulmonary hypertension (group B)

Case	Age (years)	Sex	CTR	Liver* (cm)	Treatment	
					Digitalis	Diuretics
Group A.						
1	8	F	0.58	1	-	-
2	13	M	0.50	1	-	-
3	12	M	0.56	2	-	+
4	12	M	0.53	NE	-	-
5	8	M	0.60	1	-	-
6	14	F	0.53	NE	-	-
7	9	F	0.58	2	+	+
8	10	F	0.59	NE	-	-
Group B.						
9	11	F	0.62	1	-	-
10	8	F	0.59	3	+	+
11	12	M	0.63	3	+	+
12	14	F	0.60	1	+	+
13	10	M	0.58	2	+	+
14	8	M	0.57	1	-	-

*Centimetres below right costal margin.

CTR, cardiothoracic ratio; NE, no enlargement.

lead were recorded by a CGR 1000 apparatus at a paper speed of 50 mm/s. Blood samples from the aorta, pulmonary artery, left and right ventricle, right atrium, and superior and inferior vena cava were drawn to measure oxygen saturation and content. Oxygen consumption was measured by the flow-through method.¹⁵ Systemic and pulmonary

blood flows were derived from the Fick method. The pulmonary to systemic flow ratio (Qp/Qs) and systemic and pulmonary vascular resistance were then calculated by means of known formulae. All the haemodynamic and oximetric data were obtained before and 30 minutes after sublingual administration of 10 mg nifedipine. Each procedure was completed with left ventriculography that confirmed the presence of ventricular septal defect.

Patients with a mean control pulmonary artery pressure ≤ 20 mm Hg were assigned to group A (n = 8) and those with mean control pulmonary artery pressure > 20 mm Hg to group B (n = 6).

STATISTICAL ANALYSIS

A two tailed *t* test for paired observations was used to compare differences between means. *p* values of < 0.05 were considered to be statistically significant. All values are expressed as mean (SD).

Results

Tables 1 and 2 shows the clinical findings and the haemodynamic data for each patient respectively.

GROUP A

Nifedipine administration significantly reduced the mean aortic pressure from 85.1 (12.7) to 80.6 (13.1) mm Hg (*p* = 0.01) and the systemic vascular

Table 2 Haemodynamic data before (C) and after nifedipine (N) administration in patients with ventricular septal defect without pulmonary hypertension (group A) and with pulmonary hypertension (group B)

	HR (beats/min)		Ao (mm Hg)		PA (mm Hg)		RA (mm Hg)		LVEDP (mm Hg)		Qp (l/min)		Qs (l/min)		SVR (dyn.s.cm ⁻⁵)		PVR (dyn.s.cm ⁻⁵)		Qp/Qs	
Case	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N
Group A:																				
1	110	120	94	88	20	20	4.0	4.0	9	9	7.7	12.3	4.7	4.8	1515	1388	146	71	1.62	2.54
2	70	95	75	65	12	13	3.0	1.0	2	0	7.8	8.8	5.5	7.8	1049	657	108	118	1.42	1.13
3	100	135	85	78	15	14	1.9	1.3	2	4	6.7	5.6	3.4	3.8	1814	1609	156	118	1.81	1.47
4	89	120	88	88	15	18	1.0	0.0	5	5	6.4	8.9	4.7	5.7	1481	1237	125	117	1.36	1.56
5	112	128	84	84	20	25	2.5	4.5	7	8	12.0	10.8	7.9	8.1	825	597	86	95	1.52	1.31
6	120	150	72	66	13	15	2.5	3.5	5	7	6.4	7.3	4.2	3.5	1312	1419	94	104	1.52	2.08
7	84	93	73	72	12	13	3.5	3.5	6	6	9.3	12.8	6.2	7.8	941	703	52	41	1.50	1.64
8	110	130	110	104	17	14	2.5	1.3	3	3	11.2	11.2	7.6	7.0	1139	1173	100	79	1.48	1.59
Mean	99.4	121.4	85.1	80.6	15.5	16.5	2.6	2.4	4.9	5.3	8.4	9.7	5.5	6.1	1259.5	1097.0	108.4	92.9	1.53	1.67
(SD)	(17.0)	(19.4)	(12.7)	(13.1)	(3.3)	(4.2)	(0.9)	(1.7)	(2.5)	(2.9)	(2.2)	(2.5)	(1.6)	(1.9)	(332.4)	(391.8)	(33.6)	(27.6)	(0.14)	(0.45)
p	0.003		0.011		NS		NS		NS		NS		NS		0.026		NS		NS	
Group B:																				
9	100	100	100	90	70	55	6.0	4.0	8	4	10.2	9.4	3.3	4.0	2253	1713	492	434	3.05	2.31
10	86	98	90	80	76	65	7.5	7.0	12	10	7.6	9.1	3.3	4.0	2000	1460	674	583	2.30	2.27
11	96	102	82	84	70	75	2.5	5.5	7	10	3.9	3.5	4.5	5.0	1480	1264	1280	1496	0.87	0.70
12	108	120	80	70	52	34	3.8	3.2	12	12	15.2	15.6	4.3	5.4	1416	984	128	112	3.53	2.89
13	72	77	96	88	24	29	3.0	3.5	10	6	7.4	8.4	5.4	6.6	1390	1021	152	219	1.38	1.27
14	75	85	88	94	30	30	3.0	3.5	7	7	8.0	9.9	2.7	4.4	2538	1633	229	186	3.00	2.23
Mean	89.5	97.0	89.3	84.3	53.7	48.0	4.3	4.5	9.3	8.2	8.7	9.3	3.9	4.9	1846.2	1345.8	492.5	505.0	2.26	1.93
(SD)	(14.3)	(14.9)	(7.8)	(8.5)	(22.3)	(19.7)	(2.0)	(1.5)	(2.3)	(3.0)	(3.8)	(3.9)	(1.0)	(1.0)	(488.9)	(307.7)	(440.7)	(516.0)	(1.04)	(0.80)
p	0.016		NS		NS		NS		NS		NS		0.003		0.003		NS		0.032	

HR, heart rate; Ao, mean aortic pressure; PA, mean pulmonary arterial pressure; RA, mean right atrial pressure; LVEDP, left ventricular end diastolic pressure; Qp, pulmonary blood flow; Qs, systemic blood flow; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; Qp/Qs, pulmonary to systemic flow ratio.

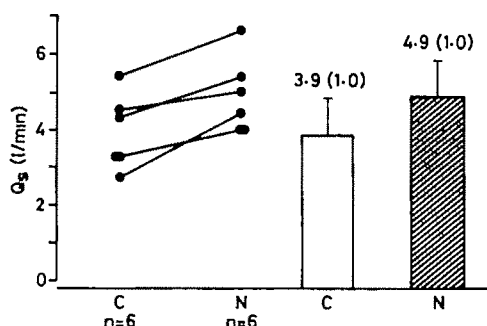


Fig 1 Effect of nifedipine on systemic blood flow in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; Q_s , systemic blood flow.

resistance from 1259.5 (332.4) to 1097.8 (391.8) dyn.s.cm⁻⁵ ($p = 0.026$); it significantly increased the heart rate (from 99.4 (17.0) to 121.4 (19.4) beats/min) ($p = 0.003$). There were non-significant changes in pulmonary vascular resistance (from 108.4 (33.6) to 92.9 (27.6) dyn.s.cm⁻⁵), cardiac output (from 5.5 (1.6) to 6.1 (1.9) l/min), stroke volume (from 57.4 (12.6) to 65.7 (29.6) ml), pulmonary blood flow (8.4 (2.2) to 9.7 (2.5) l/min), pulmonary to systemic flow ratio (from 1.53 (0.14) to 1.67 (0.45)), mean pulmonary artery pressure (from 15.5 (3.3) to 16.5 (4.2) mm Hg), left ventricular end diastolic pressure (from 4.9 (2.5) to 5.3 (2.9) mm Hg), and mean right atrial pressure (from 2.6 (0.9) to 2.4 (1.7) mm Hg).

GROUP B

In this group there were significant increases in cardiac output (fig 1) (from 3.9 (1.0) to 4.9 (1.0)

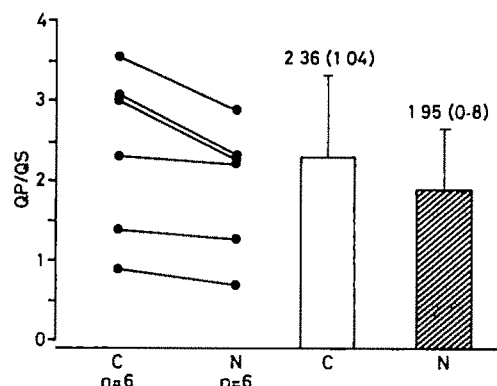


Fig 3 Effect of nifedipine on pulmonary to systemic flow ratio in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; QP/Q_s , pulmonary to systemic flow ratio.

l/min, $p = 0.005$), stroke volume (from 44.8 (15.5) to 52.0 (17.1) ml, $p = 0.02$), and heart rate (from 89.5 (14.3) to 97.0 (14.9) beats/min, $p = 0.016$) after nifedipine administration. Systemic vascular resistance fell significantly (fig 2) (from 1846.2 (488.9) to 1345.8 (307.7) dyn.s.cm⁻⁵, $p = 0.003$), as did the pulmonary to systemic flow ratio (fig 3) (from 2.36 (1.04) to 1.95 (0.80), $p = 0.032$). There were non-significant changes in mean aortic pressure (from 89.3 (7.8) to 84.3 (8.5) mm Hg), mean pulmonary artery pressure (from 53.7 (22.3) to 48.0 (19.7) mm Hg), pulmonary vascular resistance (fig 4) (from 492.5 (440.7) to 505.0 (516.0) dyn.s.cm⁻⁵), left ventricular end diastolic pressure (from 9.3 (2.3) to 8.2 (3.0) mm Hg), pulmonary blood flow (fig 5) (from 8.7 (3.8) to 9.3 (3.9) l/min), and mean right atrial

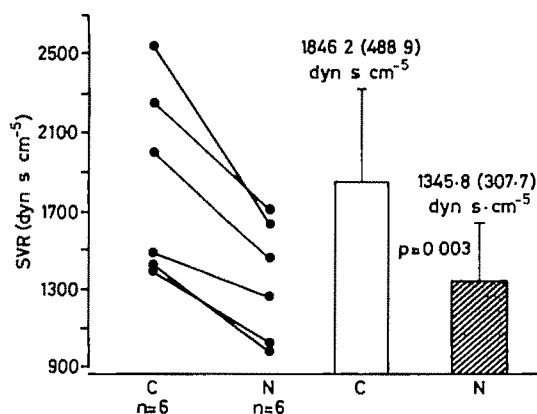


Fig 2 Effect of nifedipine on systemic vascular resistance in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; SVR, systemic vascular resistance.

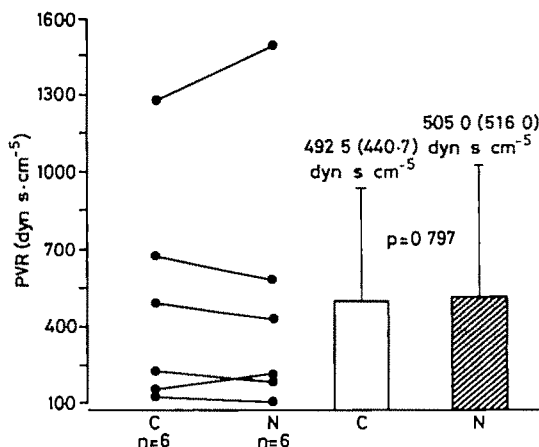


Fig 4 Effect of nifedipine on pulmonary vascular resistance in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; PVR, pulmonary vascular resistance.

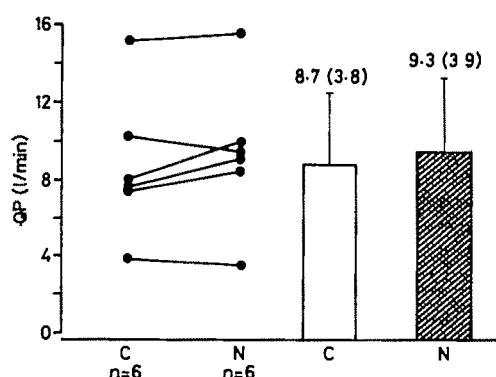


Fig 5 Effect of nifedipine on pulmonary blood flow in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; QP, pulmonary blood flow.

pressure (from 4.3 (2.0) to 4.5 (1.5) mm Hg). The only patient with a bidirectional shunt showed an increase in the right to left shunt (from 47 to 51%) after nifedipine.

Control values of systemic vascular resistance were higher in group B than in group A (fig 6) (1846.2 (488.9) v 1259.5 (332.4) dyn.s.cm⁻⁵, $p = 0.02$). Group B also showed a greater decrease in systemic vascular resistance after nifedipine (fig 7) 500.3 (232.2) v 161.6 (161.9) dyn.s.cm⁻⁵, $p = 0.007$). The magnitude of the change in systemic vascular resistance caused by nifedipine correlated well with its control value in all patients (fig 8) ($r = 0.68$, $p = 0.003$).

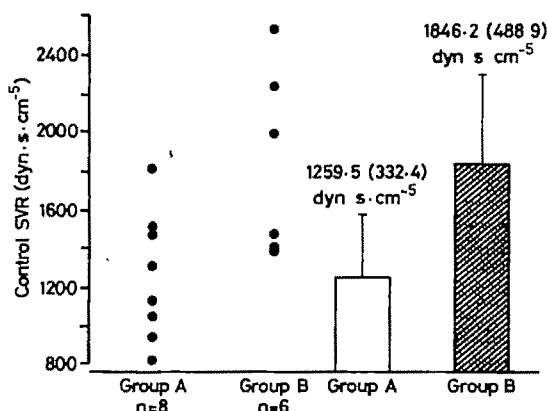


Fig 6 Comparison of control values of systemic vascular resistance between patients with ventricular septal defect without pulmonary hypertension (group A) and with pulmonary hypertension. SVR, systemic vascular resistance.

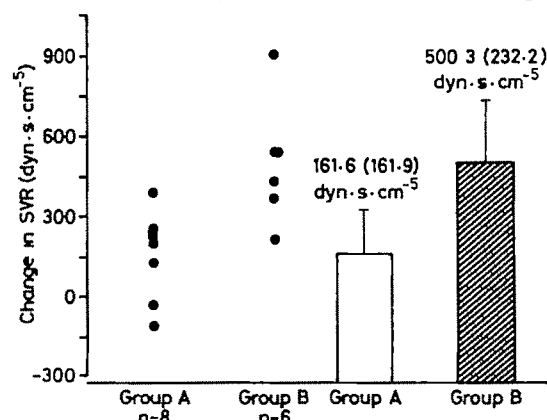


Fig 7 Comparison of changes in systemic vascular resistance caused by nifedipine between patients with ventricular septal defect without pulmonary hypertension (group A) and with pulmonary hypertension (group B) (changes are expressed as differences between control and post-treatment values). SVR, systemic vascular resistance.

Discussion

This study showed that the acute haemodynamic response to nifedipine in patients with ventricular septal defect complicated by pulmonary hypertension differs from that in patients without this complication.

After nifedipine the systemic flow and stroke volume increased and the pulmonary to systemic flow ratio decreased significantly in patients with ventricular septal defect and raised mean pulmonary

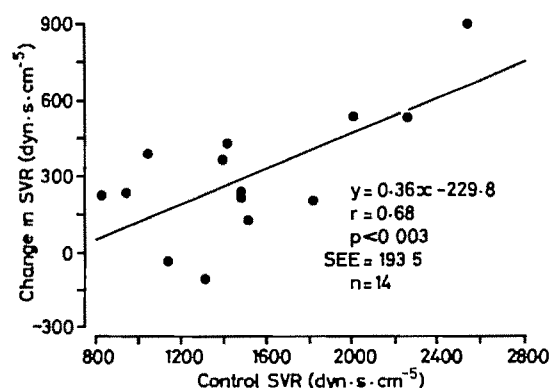


Fig 8 Relation between the control values of systemic vascular resistance and the magnitude of change after nifedipine in all the patients (changes are expressed as differences between baseline values and values after treatment). SVR, systemic vascular resistance.

arterial pressure (group B); whereas these variables did not change significantly in patients with ventricular septal defect and normal mean pulmonary artery pressure (group A). Shunting at the ventricular level, with its resultant chronic volume overload, is the basic haemodynamic anomaly in ventricular septal defect. In patients with ventricular septal defect, the haemodynamic conditions in which left ventricular emptying occurs are very similar to those created by mitral regurgitation. The defect in the ventricular septum and the regurgitant mitral valve constitute a low impedance path for a portion of cardiac output.

Lowering left ventricular afterload by means of vasodilators (hydralazine) was associated with a 50% increase in the forward stroke volume and a 33% decrease in the regurgitant volume in a group of patients with mitral regurgitation.⁴ These changes were dependent upon the extent to which systemic vascular resistance was reduced, as shown by another study of nitrates.⁵ Experimental studies of ventricular septal defect showed that the amount of interventricular shunting was largely determined by the left ventricular afterload.⁹⁻¹¹ The left to right shunt was increased by the infusion of pressor amines¹¹ and reduced (by 33%) after α blockade with phentolamine and phenoxybenzamine.⁹ A considerable decrease was seen after hydralazine administration and even more with prazosin.¹⁰ In clinical studies too hydralazine significantly increased the systemic blood flow in patients with a large ventricular septal defect.¹²⁻¹⁴ Vasodilators do not have a constant action on systemic vascular resistance, pulmonary flow, and pulmonary to systemic flow ratio. Several studies of vasodilator treatment reported increased systemic flow and reduced pulmonary to systemic flow ratio.¹²⁻¹⁴ In other studies these measurements did not change or changed in only some cases.^{14,16} Indeed there are reports of a significant increase in pulmonary to systemic flow ratio and systemic vascular resistance in response to these agents.^{17,18} The results of these studies and ours demonstrate that patients with ventricular septal defect can react in various ways to vasodilator drugs. Their response seems to be determined by several factors: the type and size of the defect itself,^{9,10} the values of systemic and pulmonary vascular resistance, and in particular the left ventricular preload and performance.¹⁶⁻¹⁸

In patients with congestive heart failure of various causes vasodilators improve left ventricular ejection and augment cardiac output by reducing the raised systemic vascular resistance; this mechanism, however, may not be active in all cases of ventricular septal defect: it is probably absent in those patients with ventricular septal defect who have normal systemic vascular resistance and left ventricular

performance¹² as did most of group A patients in our study (these indices were normal in five of our eight patients). In fact, in group A patients nifedipine substantially reduced systemic vascular resistance (which was normal in this group as a whole) and mean arterial pressure, increased heart rate without appreciably altering systemic and pulmonary blood flow, pulmonary to systemic flow ratio, mean pulmonary arterial pressure, or pulmonary vascular resistance. Furthermore, systemic vascular resistance was reduced in this group, but this reduction was probably insufficient to induce a significant change in the pulmonary to systemic flow ratio. On the other hand, this group had normal control values for pulmonary vascular resistance. This mechanism is important, however, in patients with ventricular septal defect and abnormally raised systemic vascular resistance.^{14,16} Evidence from experimental and clinical studies showed that in patients with small and restrictive ventricular septal defects and normal pulmonary vascular resistance, the amount of the left to right shunt was related to the size of the defect and to the level of systemic vascular resistance; the shunt was augmented by raising the systemic vascular resistance with pressor amines¹¹ and lowered by decreasing the raised systemic vascular resistance with vasodilators.^{10,12} This effect was seen in patient 9, who had a ventricular septal defect of moderate size with raised systemic vascular resistance and normal pulmonary vascular resistance. Nifedipine induced a consistent increase in systemic blood flow and a reduction in the pulmonary to systemic flow ratio, owing to a fall in systemic vascular resistance. By contrast, in patients with a large and non-restrictive ventricular septal defect, the amount of the interventricular shunt was primarily dependent on the pulmonary to systemic resistance ratio¹⁹⁻²¹; the effects of vasodilators in these patients are therefore determined by the responsiveness of the pulmonary and systemic circulation to these agents. A greater pulmonary to systemic vascular resistance ratio will be associated with a smaller left to right shunt, assuming all other factors remain constant.¹⁷

Vasodilator drugs dilate the systemic and pulmonary vascular bed in patients with congestive heart failure of various aetiologies.¹⁻³ Their effect in the pulmonary circulation is not, however, constant. Nifedipine and other vasodilators do not always succeed in lowering pulmonary vascular resistance²²; indeed in other studies an increase has been seen.²³⁻²⁵ This was present in patients 3 and 5 in group B. In patients with large ventricular septal defects, raised pulmonary vascular resistance (owing to functional changes), and normal or slightly increased systemic vascular resistance, vasodilator drugs may affect the pulmonary vascular bed more than the systemic one,

thereby increasing the left to right shunt. Similar evidence was derived from studies with nitroprusside^{17,18} and hydralazine.¹⁶ The same effect was seen in our patient 7 in whom nifedipine reduced systemic vascular resistance but also reduced pulmonary vascular resistance by 50%, thus increasing the left to right shunt. Preload reduction is important in the increase of pulmonary to systemic flow ratio caused by nitroprusside.¹⁷ Patients with ventricular septal defect, abnormally raised systemic vascular resistance, and reduced systemic blood flow will respond differently to vasodilators, particularly if the pulmonary vascular bed does not react to these agents because of fixed obstructive structural changes. It is the magnitude of reduction of the systemic vascular resistance that determines the decrease in pulmonary to systemic flow ratio and the increase of systemic blood flow in response to vasodilators in this group of patients. Nifedipine considerably reduced systemic vascular resistance, increased systemic blood flow and stroke volume, and reduced the pulmonary to systemic flow ratio in patients with pulmonary hypertension (group B). In this group of patients pulmonary blood flow did not change and, unlike patients without pulmonary hypertension (group A), neither did mean aortic pressure. The increases in systemic blood flow and venous return seem to have prevented the decrease of pulmonary blood flow and mean aortic pressure even in the presence of a reduced left to right shunt and reduced systemic vascular resistance.

The increase in systemic blood flow and venous return seem to have prevented both the diminished left to right shunt from reducing pulmonary blood flow and reduced systemic vascular resistance from lowering mean aortic pressure. The appreciable reduction in systemic vascular resistance was responsible for the significant increase of systemic blood flow and decrease of pulmonary to systemic flow ratio in our patients because in both groups neither pulmonary vascular resistance nor the left and right ventricular preload showed any significant change in response to nifedipine.

Our study shows that the magnitude of reduction of the systemic vascular resistance by nifedipine in our patients was a function of the pretreatment value because (a) the decrease in systemic vascular resistance was significantly greater in group B (in which systemic vascular resistance was higher) than in group A, and (b) the size of the change in systemic vascular resistance after nifedipine correlated well with its control value. A similar correlation was shown in other studies of vasodilators in patients with congenital or acquired heart disease. In a group of patients with valvar regurgitation the reduction in systemic vascular resistance by nitrates was more

pronounced in those with higher control values.³ In another study in patients with large ventricular septal defect and pulmonary hypertension hydralazine caused a larger decrease in systemic vascular resistance (29%) in patients with systemic vascular resistance of $> 20 \text{ units.m}^2$ than in patients with systemic vascular resistance $< 20 \text{ units.m}^2$ (only 6%).¹⁴

We conclude that in patients with ventricular septal defect and pulmonary hypertension, nifedipine significantly reduced Qp/Qs and substantially increased systemic blood flow; this had a beneficial effect on the fundamental haemodynamic disturbance in patients with a left to right shunt. Nifedipine exerts its haemodynamic effect by lowering systemic vascular resistance.

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Propranolol treatment in children with tetralogy of Fallot alters the response to isoprenaline after surgical repair

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SUMMARY When propranolol is given to prevent hypoxaemic episodes in children with tetralogy of Fallot who are awaiting operation it is advisable to continue the treatment until shortly before the induction of anaesthesia. Because catecholamines are often required to maintain adequate cardiac output after surgical correction the effect of preoperative treatment with β blockers on the response to isoprenaline after the operation was investigated in nine children given propranolol before operation and nine who were not. They were studied three and 24 hours after cardiopulmonary bypass. The haemodynamic response to increasing doses of infused isoprenaline was monitored. Immediately after cardiopulmonary bypass the response to isoprenaline was significantly blunted in the patients who had been given propranolol before operation. Their dose-response curve lay to the right of that for patients not given propranolol, and this indicates competitive inhibition. Propranolol concentrations in the blood and myocardium correlated significantly with the heart rate response to isoprenaline. Twenty four hours after operation the isoprenaline response was similar in both groups and concentrations of propranolol in the blood were minimal or undetectable.

β Blockers given up to the time of operation significantly altered the postoperative response to catecholamines.

Propranolol is a β adrenergic blocking drug that is used to prevent hypoxaemic episodes in children with Fallot's tetralogy who are awaiting surgical correction.¹⁻³ To prevent anoxic spells at the induction of anaesthesia, we withdraw propranolol only the night before the operation. We use isoprenaline to sustain cardiac output after open heart surgery for tetralogy of Fallot, because these patients rely mainly on heart rate to increase their cardiac index.⁴ Persistence of β adrenergic blockade after cardiopulmonary bypass could be clinically important in these patients.

The present study was designed to investigate whether propranolol given up to the night before

the operation alters the response to adrenergic drugs given immediately after operation.

Patients and methods

Between June 1985 and April 1986, 18 patients aged 10 months to 12 years were studied immediately after surgical correction of tetralogy of Fallot. Nine patients (group 1) had been treated with daily doses of propranolol for at least two weeks before operation (1.5 to 4 mg/kg/per day). Propranolol was given every six hours until the night before induction of anaesthesia. The nine other patients (group 2) were not given β blocking drugs before operation.

Two patients in group 2 had pulmonary stenosis with atrial septal defect, all the others had typical tetralogy of Fallot. Table 1 shows the patients' characteristics and haemodynamic data at cardiac

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Table 1 Patients' characteristics and haemodynamic data at cardiac catheterisation (mean (SD))

	Group 1 (n = 9)	Group 2 (n = 9)	p
Age (yr)	3.5 (2.1)	7.5 (4.8)	<0.05
Weight (kg)	12.2 (4.2)	22.9 (12.2)	<0.05
Haematocrit (%)	55.4 (7.1)	49.4 (9.5)	NS
CPB (min)	122.6 (15.3)	112.7 (46.0)	NS
Aortic cross clamping (min)	75.4 (35.8)	81.1 (10.2)	NS
Aortic saturation (%)	59.5 (15.4)	82.7 (7.5)	<0.05
EDVI (l/m ²)*	71.4 (47.0)	70.7 (33.1)	NS
EF (%)*	60.3 (3.9)	56.3 (8.9)	NS

*Volume and ejection fraction available in six patients from group 1 and seven from group 2.

CPB cardiopulmonary bypass, EDVI, end diastolic volume index, EF, ejection fraction

catheterisation. The control group was significantly older and had a higher mean arterial oxygen saturation. Two patients in group 2 had palliative shunts (left aorto-pulmonary artery anastomosis with a Goretex tube). Both shunts were functioning at the time of operation. Preoperative ventricular function was similar in both groups as assessed by ventricular end diastolic volume index and ejection fraction calculated from biplane cineangiography. The operation was performed under cardiopulmonary bypass, deep hypothermia (18°C), and moderate haemodilution (haematocrit 28%). Cardiopulmonary bypass and aortic cross clamping time were similar for the two groups (table 1). Cold chemical cardioplegia was used to obtain asystole before right ventriculotomy, resection of the muscular hypertrophy, enlargement of the outflow tract, and closure of the ventricular septal defect. Five patients required a transannular enlargement of the pulmonary artery.

The study started 3–4 hours after closure of the chest when the patients were in a stable haemodynamic condition in the intensive care unit. No volume expansion was needed during the study. Heart rate, central venous pressure, systolic, mean and diastolic systemic arterial pressures, and left atrial pressure were measured with a 78353-B Hewlett-Packard pressure module. Left atrial pressure was monitored through a surgically placed line.

We assessed the degree of β blockade after cardiopulmonary bypass by measuring the dose-response curves for isoprenaline three and 24 hours after operation and correlating them with blood and tissue concentrations of propranolol. All medications were stopped 20 minutes before baseline measurements. Isoprenaline was then administered continuously at increasing doses: 0.025, 0.05, and 0.1 $\mu\text{g/kg}$ per minute. Each dose was maintained for 15 minutes before a new set of measurements was

taken. Twenty minutes after the drug had been stopped a second set of baseline values was measured. The same protocol was repeated 24 hours later.

Blood propranolol concentrations were measured at four different times: (a) immediately before the last dose given before operation (steady state level); (b) after induction of anaesthesia, immediately before cardiopulmonary bypass—that is about eight hours after the last dose; (c) three hours after cardiopulmonary bypass—that is at the beginning of the first study; (d) 24 hours after cardiopulmonary bypass, at the start of the second study period. Propranolol concentrations were measured in myocardium excised from the infundibulum during the operation. Samples were immediately frozen at -80°C in liquid nitrogen and homogenised.

Concentrations of propranolol in blood and tissue were measured by high pressure liquid chromatography with fluorometric detection.³ All results are expressed in ng/ml of total blood and ng/g of myocardium (wet tissue weight).

The protocol of the study was approved by the ethics committee of our department.

STATISTICAL ANALYSIS

Unpaired and paired *t* tests were used to compare data between the two groups. Two way analysis of variance was performed on the haemodynamic results. We used semi-logarithmic regression to compare blood and tissue concentrations with haemodynamic data and Spearman's ρ coefficient to compare tissue and blood concentrations.

Results

Baseline haemodynamic data before isoprenaline were not significantly different in the two groups on either the first or second days (tables 2 and 3).

ISOPRENALINE DOSE-RESPONSE CURVE THREE HOURS AFTER CARDIOPULMONARY BYPASS

The heart rate increased in both groups on each of the three doses of isoprenaline, however, the increases were significantly less in the group treated with propranolol (group 1): group 1: +5%, +14%, +33%; group 2: +20%, +41%, +51%. The two groups had parallel dose-response curves with the curve for group 1 being shifted to the right (fig 1).

Central venous pressure and left atrial pressure fell significantly in both groups during isoprenaline infusion but they returned to baseline values as soon as the drug was stopped. Diastolic arterial pressure was significantly reduced on the third dose of isoprenaline in group 2, whereas it increased significantly on the three doses of isoprenaline in group

Table 2 Haemodynamic response (mean (SD)) to isoprenaline (ISP $\mu\text{g/kg}$ per min) immediately after cardiopulmonary bypass in patients treated with propranolol before operation (group 1) and in those who were not (group 2)

	Baseline 1	ISP 0.025	ISP 0.05	ISP 0.1	Baseline 2
Group 1:					
HR (beats/min)	118.5 (19.1)	125.3 (23.3)**	135.2 (27.6)**	157.1 (28.3)**	118.5 (18.4)
CVP (mm Hg)	12.1 (3.2)	10.8 (2.9)	10.3 (2.3)*	10.4 (2.6)*	11.8 (2.6)
LAP (mm Hg)	14.3 (3.5)	13.1 (3.8)	12.4 (4.0)*	10.6 (3.3)**	13.9 (3.9)
SAP (mm Hg)	83.1 (11.3)	90.8 (9.7)**	96.2 (11.1)**	98.8 (10.8)**	86.1 (9.6)
DAP (mm Hg)	55.7 (9.2)	60.8 (7.2)**	64.1 (10.3)**	63.9 (10.3)**	59.8 (9.3)
MAP (mm Hg)	67.2 (10.3)	72.4 (7.5)	76.9 (11.3)**	76.5 (11.1)**	70.1 (9.2)
Group 2:					
HR (beats/min)	118.3 (24.4)	142.0 (25.2)**	166.2 (16.8)**	179.8 (17.6)**	126.2 (21.7)
CVP (mm Hg)	11.9 (2.9)	10.9 (3.2)	10.1 (3.5)*	9.6 (4.0)*	11.7 (3.8)
LAP (mm Hg)	11.8 (2.7)	10.8 (2.5)	9.3 (3.0)**	8.8 (3.1)**	12.3 (2.8)
SAP (mm Hg)	77.6 (25.8)	83.8 (23.8)	86.4 (28.6)*	80.6 (24.4)	80.6 (21.5)
DAP (mm Hg)	53.6 (17.5)	54.0 (13.3)	52.3 (13.9)	46.9 (9.6)*	55.2 (13.3)
MAP (mm Hg)	62.0 (19.7)	63.9 (15.8)	62.6 (17.5)	59.3 (12.9)	64.3 (15.3)

HR, heart rate; CVP, central venous pressure; LAP, left atrial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure.

* $p < 0.05$ and ** $p < 0.01$ compared with baseline 1

Table 3 Haemodynamic response (mean (SD)) to isoprenaline (ISP $\mu\text{g/kg}$ per min) 24 hours after cardiopulmonary bypass in patients treated with propranolol before operation (group 1) and in those who were not (group 2)

	Baseline 1	ISP 0.025	ISP 0.05	ISP 0.01	Baseline 2
Group 1					
HR (beats/min)	120.3 (11.4)	135.8 (17.5)**	148.8 (22.2)**	168.2 (22.0)**	126.2 (11.6)
CVP (mm Hg)	12.3 (2.1)	11.5 (1.9)	9.8 (1.8)**	8.6 (1.8)**	11.0 (2.4)
LAP (mm Hg)	14.0 (3.6)	12.0 (4.4)*	10.0 (3.1)**	8.9 (3.0)**	11.2 (3.3)
SAP (mm Hg)	71.4 (10.1)	77.0 (14.3)	82.8 (15.7)**	83.3 (13.0)**	70.1 (12.6)
DAP (mm Hg)	50.4 (8.6)	51.8 (8.8)	53.6 (9.9)	50.3 (9.9)	48.9 (10.3)
MAP (mm Hg)	57.9 (9.2)	61.2 (9.4)	63.1 (10.6)	60.2 (9.5)	56.8 (10.1)
Group 2					
HR (beats/min)	118.3 (16.6)	134.4 (15.9)**	149.1 (20.5)**	167.9 (13.3)**	124.9 (16.7)
CVP (mm Hg)	13.3 (3.4)	12.2 (4.8)	11.4 (5.8)	11.7 (4.8)	12.2 (4.7)
LAP (mm Hg)	16.2 (4.8)	14.0 (5.4)	12.0 (5.7)*	12.3 (2.6)*	15.0 (3.7)
SAP (mm Hg)	75.8 (13.8)	83.7 (14.8)	83.9 (11.4)*	94.9 (18.1)**	81.2 (10.7)
DAP (mm Hg)	53.2 (10.9)	55.2 (7.9)	53.1 (7.5)	55.4 (11.1)	55.8 (8.5)
MAP (mm Hg)	62.0 (11.6)	65.3 (9.0)	64.0 (8.8)	67.9 (12.9)*	64.3 (9.8)

* $p < 0.05$ and ** $p < 0.01$ compared with baseline 1

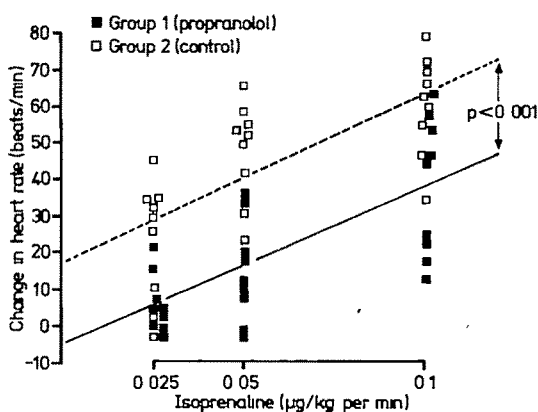


Fig 1 Heart rate response to isoprenaline three hours after cardiopulmonary bypass in patients who had been treated with propranolol and those who had not (group 1: $y = 428(x) - 4$; group 2: $y = 470(x) + 17$).

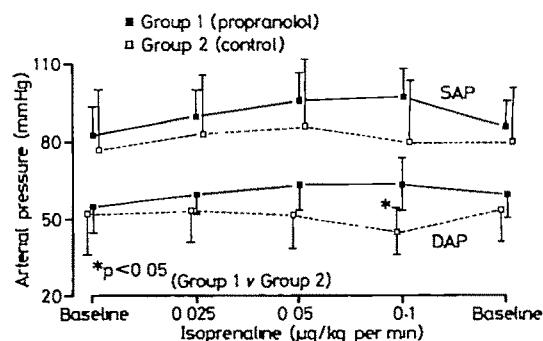


Fig 2 Mean (SD) systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) responses to isoprenaline three hours after cardiopulmonary bypass in patients who had been treated with propranolol (group 1) and those who had not (group 2).

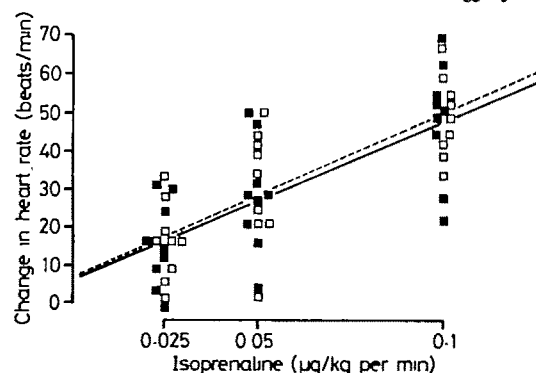


Fig 3 Heart rate response to isoprenaline 24 hours after cardiopulmonary bypass in patients who had been treated with propranolol and those who had not (group 1: $y = 426(x) + 6$; group 2: $y = 431(x) + 7$).

1 (patients given propranolol before operation) (fig 2).

DOSE-RESPONSE CURVE FOR ISOPRENALINE 24 HOURS AFTER CARDIOPULMONARY BYPASS

There were similar increases in heart rate in both groups (group 1: +12.5%, +23%, +40%; group 2: +13.5%, +26%, +41%). Figure 3 shows that the

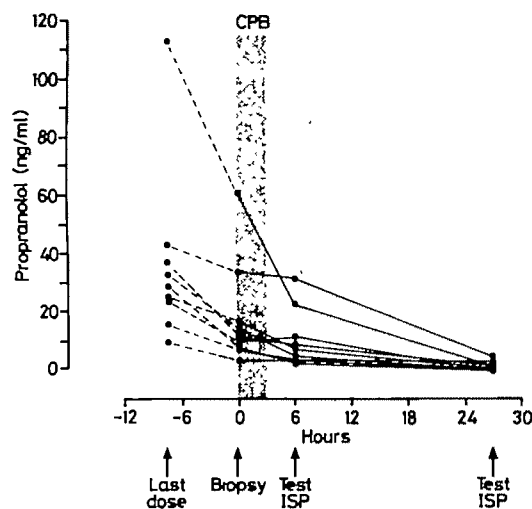


Fig 4 Change in serum concentrations of propranolol with time. The first blood sample was taken just before the last dose of propranolol was given. The second sample was taken before cardiopulmonary bypass, the third sample at the beginning of the first isoprenaline (ISP) study (three hours after cardiopulmonary bypass (CPB)), and the last sample at the time of the second isoprenaline study (24 hours after cardiopulmonary bypass). A myocardial biopsy specimen was excised from the infundibulum during cardiopulmonary bypass.

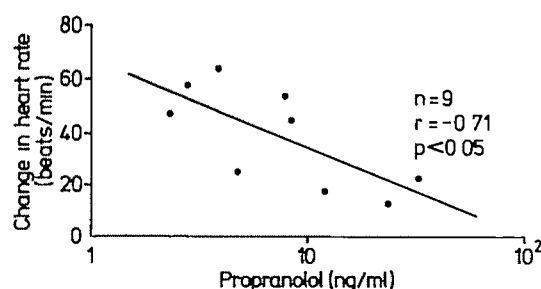


Fig 5 Inverse relation between heart rate response to 0.1 µg/kg per min of isoprenaline and serum concentration of propranolol. ($y = -34(\log x) + 68$)

dose-response curves for both groups are now superimposed.

Central venous pressure fell significantly in group 1 only, whereas left atrial pressure was significantly reduced in both groups. There was no significant difference in systolic and diastolic arterial pressures between the two groups.

PROPRANOLOL CONCENTRATIONS

The mean steady state propranolol concentration in blood was 37 ng/ml (range 10–110 ng/ml). Immediately before cardiopulmonary bypass—that is eight hours after the last dose of propranolol—the mean blood concentration had decreased to 18.7 ng/ml (range 3.4–61.5 ng/ml).

At the time of the first isoprenaline study, propranolol was still detectable in the blood (mean 10.8 ng/ml, range 2.3–32.2 ng/ml). Twenty four hours later, however, propranolol was undetectable in three patients and ranged from 1 to 5.6 ng/ml in the others (fig 4).

There was no correlation between steady state blood concentrations of propranolol and the dose administered. There was a significant inverse correlation between blood concentrations of propranolol and the chronotropic response to the

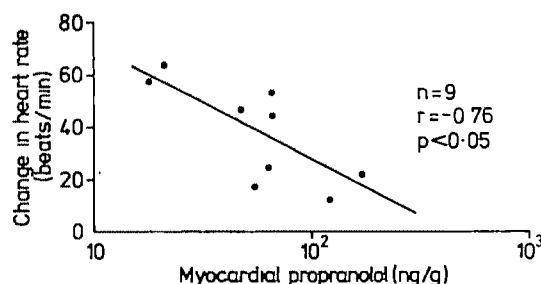


Fig 6 Inverse relation between heart rate (HR) response to 0.1 µg/kg per min of isoprenaline and myocardial concentration of propranolol ($y = -45(\log x) + 118$).

highest dose (0.1 µg/kg per minute) of isoprenaline ($r = -0.71$, $p < 0.05$) (fig 5).

Myocardial propranolol concentrations ranged from 17.8 to 169 ng/g of tissue and were 3–5 times higher than blood concentrations. There was a significant inverse correlation between myocardial concentrations of propranolol and the chronotropic response to 0.1 µg/kg per minute of isoprenaline ($r = -0.76$, $p < 0.05$) (fig 6).

There was a highly significant correlation between blood concentrations of propranolol measured immediately before cardiopulmonary bypass and myocardial concentrations ($r = 0.93$, $p < 0.001$). One patient from group 1 had a hypoxaemic episode when anaesthesia was induced; this was controlled by an injection of intravenous morphine.

Seventeen of the 18 patients made a good recovery. In one (group 2) mumps developed three days after operation and he became comatose. This encephalopathy was not caused by hypotension or an electrolyte imbalance. He died 14 days after operation. Necropsy was not performed.

Discussion

The question of when to withdraw β blocking treatment before operation was prompted by several postoperative deaths in adults that were supposedly related to β blockade.⁶ These led to the recommendation that propranolol should be stopped two weeks before operation. But subsequent studies suggested that propranolol treatment could be continued until shortly before operation. Faulkner *et al* showed that propranolol was undetectable in plasma samples and atrial tissue 36–48 hours after withdrawal of the drug,⁷ whereas Romagnoli and Keats showed that although propranolol was still detectable in plasma samples and atrial tissue 18 hours after the drug was stopped no β blocking effects could be demonstrated at that time.⁸

We found that when propranolol was given up to the night before operation it persisted in the blood and in myocardium after cardiopulmonary bypass and modified the response to isoprenaline immediately after operation. The degree of β blockade can be assessed by measuring the acceleration of heart rate induced by isoprenaline.^{9–11} In the present study, the different chronotropic response to isoprenaline immediately after cardiopulmonary bypass indicated the persistence of significant β blockade in group 1. The rightward shift of the dose-response curve indicates competitive inhibition of the chronotropic effect of isoprenaline.

The response of diastolic arterial pressure to isoprenaline in the two groups was different and this suggests that propranolol, as well as inhibiting the

heart rate response to isoprenaline, also inhibits its systemic vasodilator effect.

In adults the response of heart rate to exercise after oral propranolol is most strongly blocked at blood concentrations of 40 ng/ml.¹² The steady state concentrations of propranolol in our patients are consistent with maximum β blockade. Somewhat surprisingly, there was no relation between the oral dose of propranolol and steady state blood concentrations in our patients. The concentrations immediately before cardiopulmonary bypass were lower, probably because of the longer interval after the last dose. None the less, a mild haemodilution related to induction of anaesthesia could have had a role. We found a linear correlation between the logarithm of plasma propranolol and the degree of β blockade (assessed by heart rate response to isoprenaline infusion), which confirmed the results of a previous study.¹³

Several workers have studied blood concentrations of intravenously administered propranolol before and after cardiac surgery.^{14,15} Plachetka *et al* found that propranolol concentrations were higher after cardiopulmonary bypass than before. They suggested that this was the result of a redistribution of the drug from the lungs to the plasma and of a reduced hepatic extraction.¹⁶ McAlister *et al* explain this phenomenon by the reduction of the volume of distribution caused by hypothermia.¹⁷

Twenty four hours after cardiopulmonary bypass, a β blocking effect was no longer seen in the propranolol treated group—the responses of the two groups to isoprenaline were similar. Propranolol concentrations measured at that time were minimal or undetectable.

We conclude from our study that propranolol treatment given up to the night before the operation influences the response to isoprenaline immediately after operation. Significant concentrations of propranolol persist in the blood and myocardium for several hours after cardiopulmonary bypass and result in a blunted response to catecholamines. Despite these findings, we advocate the administration of propranolol up to the time of the operation to avoid hypoxaemic episodes during induction of anaesthesia. The residual β blockade can be overcome by the administration of higher than usual doses of catecholamines.

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Pericardiocentesis and systemic cytotoxic chemotherapy in the management of cardiac tamponade secondary to disseminated breast carcinoma

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SUMMARY Three patients with cardiac tamponade secondary to disseminated breast carcinoma were treated by pericardiocentesis followed by systemic cytotoxic chemotherapy. This approach controlled pericardial effusion in all the patients and extended their survival.

Neoplastic cardiac tamponade is one of the emergencies of clinical oncology. It is a potential life threatening complication of disseminated malignant disease and can cause sudden death. The outlook in general is appalling, and despite treatment many patients survive for only 4-5 months.¹ The choice of appropriate therapy can be difficult and the optimal management remains controversial. Vigorous treatment is often not suitable for patients who are debilitated with advanced cancer and haemodynamically compromised. None the less, in tamponade secondary to metastatic breast cancer, a vigorous approach is indicated because breast carcinoma is a potentially controllable disease for which there is effective systemic treatment. We present three cases of proven malignant cardiac tamponade secondary to disseminated breast carcinoma that we treated by pericardiocentesis followed by systemic cytotoxic chemotherapy.

Patients and methods

From 1981 to 1985, 722 new patients with breast carcinoma were seen at the Department of Radiotherapy and Oncology, Plymouth. In three (0.4%) patients clinically significant malignant pericardial effusion developed with symptoms and signs of cardiac tamponade. All three patients had dissemin-

ated breast carcinoma when tamponade developed. The diagnosis of cardiac tamponade was made on clinical examination, chest x ray, and electrocardiogram and was confirmed by echocardiography. All the patients underwent percutaneous pericardiocentesis for diagnostic and therapeutic purposes. Afterwards they were given systemic cytotoxic chemotherapy as outpatients and their response was monitored by following their clinical condition, serial chest x rays, and echocardiograms. The treatment was well tolerated with minimal side effects. In one of our patients early vinca neuropathy developed and there was no cardiotoxicity with doxorubicin in the dosage used (total dose less than 550 mg/m²). Survival was calculated from the date of pericardiocentesis to the date of death.

Results

The table shows the characteristics of our patients. All our patients were post-menopausal, the average age when cardiac tamponade developed was 58.3 years. The mean interval between diagnosis of breast carcinoma and development of tamponade was 32.7 months (range 0 to 70 months). None of our patients had previous cytotoxic chemotherapy and patients 1 and 3 had previous endocrine treatment. All our patients had evidence of metastatic disease at sites other than the pericardium when the effusion presented. The pericardial aspirate (mean volume 716 ml (range 150-1350 ml)) in all the cases was an exudate containing adenocarcinoma cells. The mean survival was 14.7 months (range 14 to 16 months). In all the

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Table 1 Patient characteristics

Patient No	Age at diagnosis of cardiac tamponade (yr)	Interval between diagnosis of breast cancer and development of cardiac tamponade (mth)	Previous treatment	Post-pericardiocentesis systemic chemotherapy	Survival (mth)	Cause of death
1	57	70	Surgery, palliative radiotherapy, hormones	Doxorubicin, vincristine, and prednisolone	14	Braun, lung, and bone metastases
2	69	At presentation	Nil	Doxorubicin, vincristine, and prednisolone *Doxorubicin, 5-fluorouracil and prednisolone	14	Bone and pleural metastases
3	49	28	Surgery, loco-regional radiotherapy, artificial menopause, hormones	Doxorubicin, vincristine, and prednisolone *Mitomycin-C, 5-fluorouracil, vindesine, and prednisolone	16	Lung, pleural, and intra-abdominal metastases

*Chemotherapy regime is altered because of progression of disease at sites other than the pericardium

patients death was caused by progressive metastatic disease and the pericardial effusion did not recur.

Discussion

The accumulation of fluid in the pericardial space in patients with cancer is often not recognised until cardiac tamponade develops. The fluid usually reaccumulates rapidly after pericardiocentesis unless further definitive treatment is started. Such alternatives include the insertion of a pleuro-pericardial window,² total or partial pericardiectomy,³ external radiotherapy,⁴ local instillation of a chemotherapeutic agent,⁵ local instillation of a sclerosing agent,⁶ and systemic chemotherapy.⁷ Press and Livingston⁸ in a recent review of documented reports of malignant pericardial effusion and tamponade noted that no definitive conclusion can be made about optimal management because there are no controlled trials and many series are small with heterogeneous distribution of tumour types, varying criteria for clinical response, and concurrent treatments.

Reynolds and Byrne advocate pericardiocentesis followed by systemic chemotherapy for malignant pericardial effusion in carcinoma of the breast.⁷ Local control of pericardial effusion was achieved and survival was extended but their survival data were incomplete. Bitran *et al* managed their patients with a pleuropericardial window and systemic chemotherapy.⁹ They achieved a median survival of 26 months (range 17–50 months). Direct comparisons are difficult but we do not believe that the establishment of a pleuropericardial window is necessary because none of our patients had evidence of recurrence of pericardial effusion at the time of death. Smith *et al* in a review of all reported cases of

malignant pericardial effusions up to 1974 concluded that patients treated conservatively without surgical intervention had a longer symptom free interval than those given a pericardial window.¹⁰

Although the survival of patients with neoplastic cardiac tamponade is in general limited,^{11,12} we believe that an active approach is warranted in those cases with tamponade secondary to breast carcinoma. Systemic cytotoxic chemotherapy after pericardiocentesis can achieve significant palliation in breast cancer, control pericardial effusion, prolong survival, with minimal toxicity, and give a good quality of life.

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Case reports

Management of a patient with Wilms's tumour extending into the right heart chambers: a case report and a review of other published reports

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SUMMARY Wilms's tumours that extend by direct intravascular spread into the right side of the heart are rare. A case of such a tumour was diagnosed by ultrasound. A one stage resection was performed on cardiopulmonary bypass and with profound hypothermic circulatory arrest. It was followed by adjunctive chemotherapy and radiotherapy. The child was alive and tumour free 18 months later. A review of 17 other similar cases indicated that multimodal treatment is justified in patients with extensive intravascular spread of Wilms's tumours.

There have been only 17 cases of right atrial extension of Wilms's tumour reported in English this century.¹⁻¹⁴ Such cases used to be regarded as inoperable. Advances in surgical techniques and adjunctive treatment have made surgical excision possible and worth while even when the disease is extensive. We report the management of a case of this type of Wilms's tumour which we believe to be the first reported from Britain, and we review earlier cases.

Case report

A five and a half year old boy was admitted with a history of lethargy and diarrhoea for three weeks and generalised abdominal pain and anorexia for one week.

On examination he was unwell with a tachycardia, tachypnoea, and leg oedema. His blood pressure was 110/70 mm Hg but the jugular venous pressure was raised with a prominent "a" wave. A systolic ejection murmur was audible at the left sternal edge. There were signs of a right pleural effusion. The abdomen was distended with considerable hepatomegaly, a mass in the left upper quadrant, and ascites.

Investigations showed a haemoglobin concentration of 142 g/l, white cell count of $15.8 \times 10^9/l$, and platelet count of $40 \times 10^9/l$. Coagulation tests showed an International Normalised Ratio of 2.1. The serum activity of alanine aminotransferase was raised (1266 IU/l). Bilirubin and renal function were normal.

Chest x ray confirmed a right pleural effusion and enlarged cardiac silhouette. Ultrasound scan confirmed the presence of ascites and a pleural effusion, and showed a grossly enlarged left kidney with distorted calyces. The inferior vena cava was occluded by tumour or thrombus that extended into the right atrium and prolapsed into the right ventricle with each cardiac cycle. A diagnosis of Wilms's tumour originating in the left kidney and extending to the inferior vena cava and right heart was made on the basis of this investigation.

Computed tomography showed that the renal mass originated in the upper pole and showed dilatation of the inferior vena cava. It did not detect extension of tumour into the right atrium. The lung fields were clear. Venography showed obstruction of the inferior vena cava and iliac veins above the internal iliac vessels with drainage via anastomotic channels to the vertebral venous system.

Real time cross sectional echocardiography confirmed the intracardiac tumour and suggested that it was mobile (figure). A skeletal survey was normal.

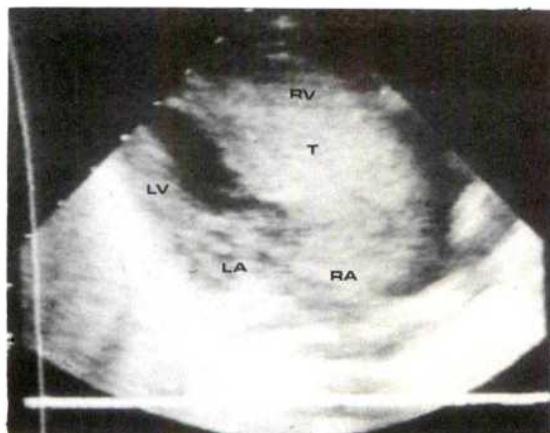


Figure Echocardiogram (apical four chamber view) showing tumour within right atrium prolapsed through to the right ventricle. T, tumour; RV, RA, LV, LA, heart chambers.

OPERATION

A cardiac team removed the intravascular tumour and an abdominal team performed the radical nephrectomy. A routine cardiac surgical anaesthetic was given. Intravascular lines were placed to monitor arterial blood pressure, pressure in the inferior and superior caval veins, and to administer fluid. A urinary catheter was inserted. Temperature probes were placed in the nasopharynx, oesophagus, and on the tympanic membrane.

A median sternotomy was performed, the presence of a large tumour mass in the right atrium was confirmed, and the heart was prepared for cardiopulmonary bypass. The incision was then extended into a full midline laparotomy and the left renal tumour was mobilised by the second team of surgeons. The inferior vena cava, left renal vein, adrenal vein, and testicular vein all had clot and tumour extending into them. The liver was grossly congested but showed no evidence of metastases. The testicular vessels were ligated distal to any macroscopic tumour and the ureter was divided at the pelvic brim.

During the final part of the dissection haemodynamic instability developed. The patient was therefore given heparin and cardiopulmonary bypass was established with one right atrial venous cannula and an ascending aortic return. While the patient was cooled to 15°C the radical left nephrectomy was completed. The specimen weighed 260 g. The aorta was cross clamped, the circulation was arrested, and the patient was exsanguinated. The right atrium and infrahepatic vena cava were opened. The intracardiac tumour was mobile but the intracaval portion was adherent and required careful instrumentation from

above and below to free it. Fogarty extraction of distal venous thrombosis to the iliac veins was performed and the right renal vein and both pulmonary arteries were checked for clearance. The inferior vena cava and right atrium were repaired and cardiopulmonary bypass was re-established by bicaval cannulation after 37 minutes of circulatory arrest. The patient was rewarmed and came off bypass without difficulty. The chest and abdomen were closed routinely with drainage. There was no difficulty in obtaining haemostasis after reversal of the heparinisation with protamine sulphate.

The patient made an excellent postoperative recovery. Histopathology confirmed the diagnosis of Wilms's tumour of the favourable histological type. Postoperative radiotherapy was given as well as one year of chemotherapy. The patient was alive, well, and disease free 18 months after operation.

Discussion

Direct extension of Wilms's tumour into the right heart cavities is rare. In one study it occurred in 0.7% of cases of Wilms's tumour.¹⁵ The table summarises the clinical features of all 17 reported cases.

Accurate preoperative diagnosis of the extent of the tumour is required to plan the management of each case. Assessment of the inferior vena cava is important in all cases of renal tumour, and before resection of hepatic tumours also, to minimise the risk of tumour embolism at operation and allow for complete resection. The upper limit of intravascular spread needs to be defined. If the caval veins are involved the possibility of extension of the tumour to the heart must be investigated. This avoids the risk that extension to the heart will be recognised only when abdominal surgery is under way and when appropriate facilities for cardiothoracic operation may not be available. Similarly, it is important to assess the inferior vena cava for distal extension in cases of suspected right atrial tumour.⁷

In nine of the 17 reported cases an accurate diagnosis was not made before the initial operation was planned (table). One patient presented with an abdominal Wilms's tumour and the inferior vena cava was not investigated before operation.⁴ The inferior vena cava was known to be affected in two cases but no further elective investigations were undertaken to define the upper limit of intravascular extension.¹⁸ In the other eight cases, and in the case reported here, the extent of the tumour was recognised before operation. Angiography has been recommended for assessment of the intravascular spread of tumours,^{8,9,14} but this invasive procedure risks precipitating tumour embolism or cardiovascular decompensation in patients whose condition is un-

stable because the heart is affected.¹⁰ Newer imaging techniques, particularly ultrasound, are useful for non-invasive investigation.^{5,6,11,13,15} We support the use of ultrasonography, which gave better results than computed tomography in our patient.

Several surgical options are available (table). Although staged resection has been performed,^{3,10} a one stage procedure is more desirable. If the tumour has extended into the right heart, cardiopulmonary bypass is usually required. We used cardiopulmonary bypass with profound hypothermia and circulatory arrest. A median sternotomy and midline laparotomy gave good access for both surgical teams, and avoids the risk of precipitating acute right heart obstruction when a patient with a mobile atrial tumour extension is turned.^{4,16} We performed the sternotomy first to allow rapid institution of cardiopulmonary bypass in the event of haemodynamic instability. Although the whole procedure could have been performed on bypass, we elected to do as much of the dissection as possible before heparinisation to avoid the risk of excessive bleeding. Circulatory arrest allowed controlled, accurate

excision of the atrial and caval tumour in a bloodless field, and reduced the risk of tumour embolism. This phase of the resection was completed well within the safe period of circulatory arrest (45–60 minutes at 15 °C). Cardiopulmonary bypass^{13,14} and circulatory arrest^{3,10} have been used successfully before, but ours is the first reported case in which a planned one stage resection was performed on bypass, profound hypothermia, and circulatory arrest. This technique is similar to that reported in adults with renal cell carcinoma.^{17,18}

The prognosis of this type of Wilms's tumour is dependent on accurate preoperative assessment. Only two of the nine patients with an accurate preoperative diagnosis (including our case) have died^{5,9} and one of these had unresectable primary disease.⁵ The other seven were alive and well between eight months and five years after operation.^{10–14} Of the nine with inadequate preoperative assessment, only one has survived for more than six months (three years six months).³ Another review reported an increased complication rate when preoperative diagnosis was not accurate. This review included some of

Table Summary of the 17 earlier cases of Wilms's tumour extending into the right atrium

Ref No	Authors (date)	Method of diagnosis	Operation	Adjuvant treatment	Outcome
1	Nadas and Ellison (1968) (3 cases)	Necropsy	—	—	—
2	Anselmi <i>et al</i> (1970)	Necropsy	—	—	—
3	Murphy <i>et al</i> (1973)	Operation at time of nephrectomy	CPB and circulatory arrest the next day	Chemotherapy and irradiation	A and W 3 y and 6 mnth
4	Utey <i>et al</i> (1973)	Operation at time of nephrectomy	CPB and circulatory arrest after abdominal closure	Chemotherapy and irradiation	Died 3 mnth
5	Farooki <i>et al</i> (1975)	Echo and cardiac catheter	Unresectable primary	Chemotherapy and irradiation	Died
6	Farooki <i>et al</i> (1976)	Echo 6 mnth after previous nephrectomy	1 stage resection with CPB	None specified	Died 6 mnths (Ref 11)
7	Aytac <i>et al</i> (1976)	Cardiac catheter diagnosis of atrial tumour. Extension from below diaphragm only recognised at operation. Wilms's tumour diagnosed at necropsy	Atrial clearance only with CPB	—	Died
8	Schullinger <i>et al</i> (1977)	Emergency cardiac catheterisation after elective operation had been planned	1 stage resection with CPB	—	Died at operation
9	Vaughan <i>et al</i> (1977)	Cardiac catheterisation	1 stage resection with CPB via T/A incision	Chemotherapy and irradiation	Died 6 mnth
10	Theman <i>et al</i> (1978)	Cardiac catheterisation and CT scan	2 stages with CPB and circulatory arrest, and "interval nephrectomy" after 3 mnth	Chemotherapy and irradiation	A and W 19 mnth
11	Slovic <i>et al</i> (1978)	Cardiac catheterisation and CT scan	No treatment described	?	Alive 8 mnth
12	Kolmannskog <i>et al</i> (1979)	Cardiac catheterisation	1 stage resection with no CPB	Chemotherapy only	A and W 15 mnth
13	Luck <i>et al</i> (1982) (2 cases)	Echo and ultrasound	1 stage resection with CPB	Chemotherapy and irradiation	A and W 18 mnth; A and W 20 mnth
14	Schraut and Chilcote (1985)	Cardiac catheterisation	1 stage resection with CPB	Chemotherapy and irradiation	A and W 5 y

CPB, cardiopulmonary bypass; T/A, thoraco-abdominal; A and W, alive, well, disease free; CT, computed tomography.

the reported cases reviewed in the present article.¹⁵

Intravascular extension of Wilms's tumour into the right side of the heart is rare. With modern imaging techniques, particularly ultrasound, it should be possible, however, to establish a diagnosis before operation. A planned one stage resection is then feasible after a midline sternotomy and laparotomy. Cardiopulmonary bypass, with or without hypothermic circulatory arrest, is needed for excision of the intravascular tumour. Complete surgical resection followed by adjunctive chemotherapy and radiotherapy may give long term, tumour free survival.

We thank Dr Rosemary Shannon for the post-operative oncological treatment of our patient and Dr A C Lamont, Dr R Leanage, and Dr K Simpson for their valuable contributions to the management of this case.

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Mitral incompetence associated with lipoma infiltrating the mitral valve

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SUMMARY A 54 year old man presented with presyncopal symptoms. Echocardiography and subsequently computed tomography showed a mass in the posterior mitral annulus causing incompetence of the valve. At operation a lipoma was found which could not be resected. Mitral incompetence was the result of chordal rupture where the lipoma had engulfed the papillary muscle. The valve was replaced and the patient made an uneventful recovery.

This case report shows a potential danger of an otherwise benign lesion.

Primary cardiac tumours are very rare and lipomas account for about 8% of these lesions. Approximately 50% are subendocardial, 25% are subepicardial, and 25% are subpericardial. The case presented here was unusual because the lipoma, though benign and arising in the wall of the ventricle, had infiltrated both the papillary muscle and the leaflets of the mitral valve and had caused incompetence of the valve.

Case report

A 54 year old white man presented with presyncopal symptoms which had lasted for two weeks and then spontaneously resolved. He was seen by his family doctor who referred him for cardiological assessment.

Further questioning did not elicit a history of rheumatic fever or other relevant cardiac history. He did, however, remark that more than 25 years before an Army Medical Officer had spent an unusually long time on auscultation of his heart and had called for a second opinion before passing him as fit for national service. No details of that examination are available.

Physical examination showed a fit looking man with blood pressure of 130/80 mm Hg when supine and normal jugular venous pressure. All peripheral pulses were present with a regular, normal wave form. The heart was impalpable. At auscultation, a soft late systolic murmur was best heard at the left sternal edge; there was no radiation. The remainder of the physical examination, including the respiratory system, was normal.

The erythrocyte sedimentation rate was 4 mm in the first hour and the full blood count was normal with a normal white cell differential count. Biochemical tests were also normal. The electrocardiogram showed sinus rhythm (90 beats per minute), a normal cardiac axis, no ischaemic features at rest, normal P wave, PR interval 0.16 s, and no evidence of right or left ventricular hypertrophy or strain. Chest x ray showed a normal cardiothoracic ratio with a normal cardiac silhouette and clear lung fields.

The echocardiogram showed an echodense intracardiac mass approximately 2 cm in diameter, which seemed to be pedunculated and was mobile within the left ventricle. It seemed to originate from between the posterior insertion of the mitral valve and the posterior wall of the left ventricle. All other aspects of the echocardiogram were normal.

Computed tomography (figure) of contiguous sections of the heart was performed before and after the administration of intravenous contrast. This showed a rounded area (2.5 cm in diameter) with the density of fat in the left ventricle which was still present after contrast, but inconsistently so, suggesting the possibility of a mobile mass.

Angiography of the left ventricle showed a filling defect close to the posterior mitral annulus that seemed to be spreading down the posterior wall of the left ventricle. There was grade 2 mitral regurgitation with normal coronary arteries.

At operation the pericardial sac contained no fluid and there were no adhesions. There was a lipomatous mass on the posterior aspect of the left ventricle in the region of the mitral annulus. The left atrium was explored under standard cardiopulmonary bypass and cold cardioplegic arrest. This showed that the fatty tumour on the epicardial surface of the heart

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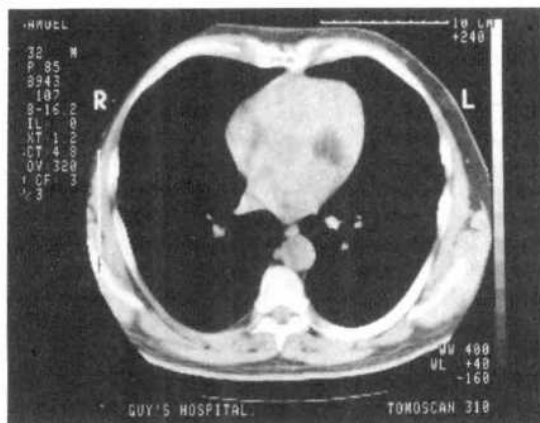


Figure Computed tomogram with contrast enhancement showing a filling defect (dark area) in the cavity of the left ventricle.

had penetrated through the posterolateral aspect of the left ventricular wall adjacent to the mitral annulus. It extended distally and subendocardially into the posterior ventricular myocardium and proximally through the mitral annulus into the floor of the left atrium. There was a patulous deformity of the lateral aspect of the mitral valve that was probably related to the anterior leaflet, though it was impossible to be certain about this because of the distortion produced by the fatty tumour at this point. In addition, there was rupture of some of the minor chordae attached to the anterior leaflet where the tumour seemed to have engulfed the anterior papillary muscle. It was impossible to excise the tumour so multiple biopsy specimens were taken. The mitral valve was excised and replaced with a bioprosthetic valve. The patient made a good recovery from the operation. When he was seen at follow up after three months he was well and ready to return to work. Repeat echocardiography showed a mass in the left ventricle as before, but reduced in size. He will be followed up by serial echocardiography.

Histology of the tissue showed a benign lipoma throughout all sections. There was myxoid change as well as infiltration by lipocytes into the anterior mitral leaflet and papillary muscle.

Discussion

Cardiac tumours are rare. The reported occurrence in two large necropsy series was 0.0017%¹ and 0.03%². Nearly half of all cardiac tumours are myxomas. Rhabdomyoma, the next most common neoplasm, is the most common childhood tumour. Fibroma, lipoma, haemangioma, and lymphangioma

are rare mesodermal tumours. Lipomas must be distinguished from lipomatous hypertrophy of the interatrial septum, which is a more common finding. Lipomatous hypertrophy of the interatrial septum is characterised by fetal fat cells, whereas lipomas contain mature lipocytes.³ Only about 25% of primary cardiac neoplasms are malignant and nearly all are sarcomas. But secondary deposits, which are 20–30 times more common than primary neoplasms,¹ are the most common cardiac tumours.

Because cardiac tumours are rare their clinical diagnosis is difficult. Atrial myxomas are said to have characteristic features on auscultation that distinguish them from stenosis of mitral or tricuspid valves,⁴ but most workers found that these features were inconsistent. In the past many cardiac tumours were found unexpectedly at operation during closed mitral valvotomy for presumed mitral stenosis.

Modern cardiac imaging techniques such as angiography, cross sectional and M mode echocardiography,^{5,6} and, most recently, computed tomography,^{7–9} allow accurate diagnosis before operation. With computed tomography it is often possible to identify the tissue type in the observed mass. Lipomas have a very low attenuation coefficient, less than –50 Hounsfield units.^{8–10} There are many reports of atrial myxomas diagnosed by computed tomography but none mentions the attenuation values of the lesion.^{11–14} Tsuchiya *et al* reported that five of six cases had lesions that were less dense than blood and the sixth had a lesion with the same density as blood.¹⁴ They also reported consistent non-homogeneity of the masses and the presence of calcification in three. Nevertheless, some radiologists are sufficiently confident about the ability of computed tomography to identify fat that they are prepared to advise conservative management in the case of lipomas.⁸

The various published reports of cardiac lipomas provide no clear indication about the natural history of this lesion. In the patient described by Behnam *et al* a cardiac lipoma was first diagnosed at the age of two but the patient did not have an operation until she was 16, when multiple lipomas of the mitral valve and papillary muscle were found.¹⁵ Total excision was achieved by mitral valve replacement. Barberger-Gateau reported similar treatment of a fibrolipoma of the mitral valve.¹⁶ We have only found one other case where total removal was possible.⁵ Most workers agree with our observation that it was impossible to achieve total excision because of the tendency of the tumour to infiltrate throughout the myocardium.⁶ The case we report is the first to show such extensive infiltration, affecting the mitral valve leaflets and papillary muscles, and extension into the floor of the left atrium. Follow up of the cases treated

by incomplete excision has not been long enough to assess the behaviour of this tumour. None the less, we know that lipomas grow slowly at other sites and can safely be left alone. The patient described by Behnam *et al* lived for 14 years without any major problems except the development of mitral regurgitation, which was probably present when the patient was first seen at the age of two. The history of our patient suggests that the tumour may have been present 25 years earlier when he was examined for national service. If this is so cardiac lipomas may be regarded as being as benign as they are at other sites—except when they affect a valve or exert pressure on surrounding normal tissue. Unlike myxomas they do not seem to generate emboli, but until they can be diagnosed with certainty many will be explored to confirm the diagnosis. Computed tomography seems to offer the possibility of accurate tissue diagnosis and may avoid operation in some patients who are poor operative risks. But until the attenuation coefficient of myxoma tissues is confidently established a biopsy is the only way to be certain of the diagnosis.

We thank Mr A K Yates and Dr D A Brennand-Roper for permission to report on their patient.

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Surgical creation of a double outlet right atrium for tricuspid valve stenosis after a Rastelli operation

JOHN E DEANFIELD, STEVEN R GUNDRY, JAROSLAV STARK

From the Cardiothoracic Unit, The Hospital for Sick Children, London

SUMMARY A patient with transposition of the great arteries, ventricular septal defect, and obstruction of the left ventricular outflow tract underwent a Rastelli repair. Stenosis of the tricuspid valve was not recognised before or during operation; this severely compromised the postoperative haemodynamic function and necessitated reoperation. Insertion of a second homograft from the right atrium to the right ventricle bypassed the stenosis and resulted in a complete recovery with maintenance of a biventricular circulation.

The Rastelli operation¹ remains the operation of choice for patients with transposition of the great arteries with a ventricular septal defect and obstruction of the left ventricular outflow tract. Preoperative assessment of the size and position of the ventricular septal defect, the size of both ventricular chambers, size and structure of both atrioventricular valves, and the pulmonary arteries is important because an abnormality of any of these structures may preclude a successful outcome.

We have recently operated upon a child with transposition of the great arteries, ventricular septal defect, and obstruction of the left ventricular outflow tract in whom assessment before and during operation did not lead to the diagnosis of tricuspid valve stenosis. This stenosis severely compromised postoperative haemodynamic function. The patient was reoperated upon early in the postoperative course once the problem was recognised, and a second homograft was inserted between the right atrium and right ventricle.

Case report

The patient was born after a normal pregnancy and delivery. Cyanosis was noted at the age of one and became progressively worse over the next few years. Transposition of the great arteries, ventricular septal defect, and obstruction of the left ventricular outflow tract were diagnosed by cardiac catheterisation and angiocardiology. When he was seven he was referred for further evaluation and operation.

Clinical examination on admission was compatible with the diagnosis. Further investigation including cross sectional echocardiography, cardiac catheterisation, and angiocardiology confirmed the diagnosis of transposition of the great arteries, ventricular septal defect, with severe subvalvar obstruction of the left ventricular outflow tract. No pressure gradients were detected between the right and left atria (table) or across the atrioventricular valves. It was decided to proceed with a Rastelli operation.

OPERATION

The operation was performed during hypothermic (20°C) cardiopulmonary bypass with aortic cross clamping (50 min) and cardioplegic protection with St Thomas' solution. The tricuspid valve could not be visualised adequately and so the annulus was not measured. This was the result of the rotation of the heart to the right. As there was no angiographic or echocardiographic evidence of a tricuspid valve

Table Pressure data at cardiac catheterisation

Pressure data	Preoperative	After Rastelli	After RA-RV conduit
RA	a = 9 v = 9 8	a = 24 v = 23 20	14
RV	87/0-8	36/4-11	23/4-14
PA	18/12/14	19/11/13	19/14/16
LA	a = 9 v = 9 8	(PCW) 9	(PCW) 10
LV	86/0-10	NE	NE
Ao	84/57/69	80/46/54	91/51/63

Pressures are given as systolic/diastolic/mean in Ao and PA, systolic/diastolic in RV and LV.

Ao, aorta; LA, left atrium; LV, left ventricle; NE, not entered; PA, pulmonary artery; PCW, pulmonary capillary wedge; RA, right atrium, RV, right ventricle.

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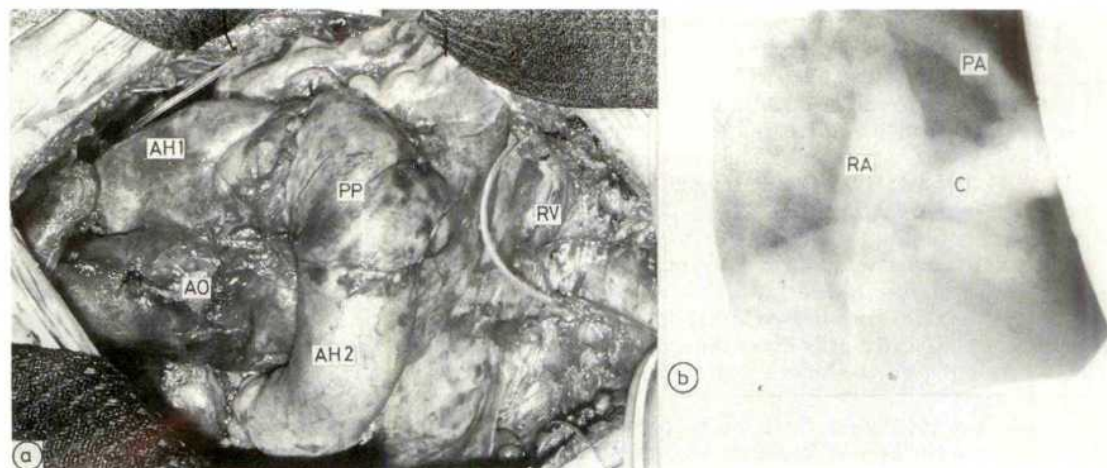


Fig 1 (a) Operative picture showing the two homografts and pericardial patch in place. AH1, first aortic homograft between the right ventricle and the pulmonary artery; AH2, second homograft between the right atrium and the right ventricle; AO, aorta; PP, pericardial patch; RV, right ventricle. (b) Angiogram showing right atrium (RA) to right ventricle conduit (C) after the second operation. PA, pulmonary artery.

abnormality no special effort was made to see the valve and measure the annulus. A right ventriculotomy was performed and a standard Rastelli procedure was carried out with a 21 mm antibiotic sterilised aortic valved homograft. At completion of the operation the right atrial pressure was raised and there was a 9 mm Hg gradient between the right atrium and the right ventricle at end diastole. The systolic gradient from the right ventricle to the pulmonary artery (17 mm Hg) was regarded as unimportant. The child was returned to the intensive care unit, intubated, and ventilated on inotropic support. His condition, however, gradually deteriorated over the next few hours and severe right heart failure with hepatomegaly and ascites developed. He went into progressive renal failure that required peritoneal dialysis. In view of the failure of medical treatment and the persistently high right atrial pressure, cardiac catheterisation was repeated (table). This confirmed the presence of a persistent gradient between the right atrium and the right ventricle at end diastole (9 mm Hg) with an additional 17 mm Hg gradient from the right ventricle to the pulmonary artery. Review of both angiocardiology and echocardiography showed that the tricuspid valve annulus was small (<95% confidence limits for the patient's body surface area), and this was felt to be the main reason for the poor haemodynamic function.

The child was returned to the operating theatre 14 hours after the completion of the first repair. The right atrium was opened on cardiopulmonary bypass with moderate hypothermia (28°C), without aortic

cross clamping. The tricuspid valve was found to be small but of normal appearance. The previous right ventricle to pulmonary artery aortic homograft was partially detached from the right ventricular outflow tract and this area was enlarged with a generous pericardial patch. A second antibiotic preserved 18 mm aortic valved homograft was then sutured with its "ventricular end" to the right atriotomy and its

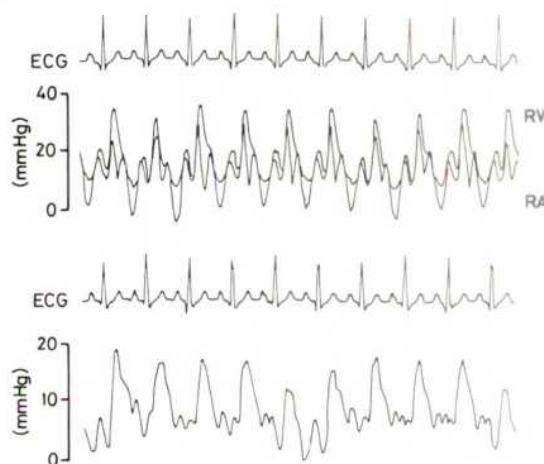


Fig 2 (Top) Pressure tracing showing no gradient at cardiac catheterisation between the right atrium and right ventricle after insertion of the right atrium to right ventricle conduit. (Bottom) A "ventricular dependent" pulmonary artery pressure tracing obtained during the same investigation.

distal end to the edges of the right ventriculotomy and the pericardial patch (fig 1a). The patient was rewarmed and bypass was stopped without difficulty. The gradient between the right atrium and right ventricle decreased to 2 mm Hg and there was no gradient between the right ventricle and the pulmonary artery. Peritoneal dialysis was stopped on the second postoperative day; the subsequent progress of the child was uneventful.

A third cardiac catheterisation was performed before the patient was discharged. This showed (table, fig 2) no gradient from the right atrium to the right ventricle and a ventricular dependent pulmonary circulation. Figure 1b shows the postoperative angiogram.

The child was discharged from the hospital on digoxin and a small dose of diuretics which were stopped after four weeks. His subsequent progress was excellent with no evidence of right or left sided heart failure over the next two years.

Discussion

Severe stenosis or hypoplasia of the tricuspid valve is one of the contraindications to the Rastelli operation.² Tricuspid valve stenosis was missed in our case both before and during operation. It is likely that the condition was not diagnosed at preoperative cardiac catheterisation because the large atrial and ventricular septal defects allowed equalisation of atrial pressures and obscured any end diastolic gradient across the tricuspid valve. The tricuspid valve had a normal configuration on both echocardiogram and direct inspection, through the ventriculotomy, and the degree of stenosis was not recognised until review at the second operation. The diagnosis became obvious after the child's condition deteriorated during the first postoperative hours, and

was confirmed at recatheterisation.

As for any other operation, the atrioventricular valve needs to be within the 95% confidence limits for the patient's body surface area. If it is smaller severe problems, such as those that developed in our patient, may occur.

There are two options when the tricuspid valve is too small. Firstly, the orifice can be closed and an atriopulmonary connection can be established (Fontan procedure).³ Secondly, the stenosis can be bypassed with a valved conduit from the right atrium to the right ventricle. We chose the second option because this had the potential of producing a biventricular circulation. This was confirmed after operation by the ventricular dependent pulmonary artery tracing (fig 2). We also felt that the second option was a simpler and shorter operation for a child in a critical condition.

This case illustrates the need for scrupulous evaluation of all patients who are to be considered for a Rastelli operation. We suggest that two conduits can be used when valvar obstruction is present at both atrioventricular and ventriculoarterial levels. We believe that this solution preserves ventricular contribution to anterograde blood flow and is preferable to an atriopulmonary connection.

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Correspondence

Blood flow patterns in the human aorta studied by magnetic resonance

Sir,

It was fascinating to see the measurements of aortic blood flow velocity obtained with magnetic resonance by Klipstein *et al* (1987;58:316-23). In the early 1970s a number of us struggled at the limits of the then available technology (mainly hot-film anemometry) to make measurements of this kind, and it is satisfying to see those results so elegantly confirmed and extended.

In only one respect are these new results at odds with previous work, and that is in the authors' conclusion that turbulence was absent. Turbulence was seen in several studies in the ascending aorta of man and several other mammalian species¹⁻³ and this is to be expected on the basis of fluid mechanics. I wonder whether this discrepancy is a matter of measurement technique?

Turbulence consists essentially of a disorganised collection of small eddies moving with the bulk flow. These cause high frequency small amplitude fluctuations in velocity that are very easily missed unless the sensing technique samples local flow and is sensitive to high frequencies. The energy content of the turbulence is small (typically less than 0.5% of the total kinetic energy in the flow) and the frequencies are high (up to several hundred Hz). Hot-film anemometer probes are ideally suited to detecting such turbulence because they are tiny and have a very high frequency response. Klipstein *et al*'s suggestion that the presence of such probes actually caused the turbulence seen in the earlier work is not, I think, plausible—flow turbulence caused in that way would only be detectable downstream, in the wake of the probe. Could an alternative explanation be that the magnetic resonance technique requires a degree of spatial or time averaging that makes it insensitive to low level turbulence?

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This letter was shown to one of the authors, who replies as follows:

Sir,

I note with interest the comments of Dr Seed, and agree with them. Despite the many advantages that we discuss in the paper, magnetic resonance velocity mapping does require both spatial and temporal averaging.

The spatial averaging is based on a typical voxel size in the region of 50 mm³ (the precise value varying both with the field of view and slice thickness). The temporal averaging arises because acquisition of the data for a series of frames takes several minutes, the images being reconstructed afterwards. The only detectable turbulence (seen as signal loss) is that which occurs repeatedly in the same place with every heart beat. High frequencies as such are not a problem because they increase the likelihood that the resultant of all velocities in the voxel over the 12 ms of data acquisition will be zero, and therefore that signal loss will occur.

The even echo rephasing that we use to retain the signal from moving blood (even though there may be a wide range of velocities passing through a single voxel) would be enough to eliminate the expected signal loss from small degrees of turbulence (as we mention at the end of the section on the principles of

magnetic resonance velocity mapping). Only gross turbulence can thus be detected by the technique. It is therefore very probable that turbulence accounting for less than 0.5% of the total kinetic energy would not be detected unless it was of large magnitude and consistently localised to a few adjacent voxels.

Within these small limitations, we feel that the convenience of magnetic resonance velocity map-

ping, particularly its non-invasiveness, opens the way to making practical a more complete understanding of the patterns of human blood flow, both normal and abnormal.

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Prediction of outcome in dilated cardiomyopathy

Sir,

A recent publication has prompted me to write concerning the diagnosis of myocarditis on endomyocardial biopsy. Diaz *et al* stated that they were "perplexed by the great increase in biopsy diagnosis of myocarditis since 1982" quoting that 21 of 39 cardiac biopsy specimens since March 1983 demonstrated "active myocarditis" or "healing" myocarditis.¹ The Dallas criteria as quoted in Dr Billingham's editorial on acute myocarditis² clearly state that the diagnosis of ongoing (persistent) myocarditis, resolving myocarditis, and resolved myocarditis can only be made after a previous biopsy specimen has shown active myocarditis. Thus it seems evident that an initial, diagnostic biopsy specimen cannot be classified as "healing" myocarditis in the absence of earlier information. The changes may have causes other than myocarditis and these could account for the apparent increase in the

diagnosis of myocarditis.

When considering myocarditis and dilated cardiomyopathy and the question of whether the former may cause the latter, it is vital that statements about biopsy specimens are accurate and that precise labels such as "healing myocarditis" are not attached to imprecise data.

Patricia J Lowry,
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Notice

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 22 to 24 November 1988. The closing date for receipt of abstracts was 24 June 1988.

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Editorial

The end of the p value?

STEPHEN J W EVANS,* PETER MILLS, JANE DAWSON

From the Departments of Clinical Epidemiology and Cardiology, The London Hospital; and the British Heart Journal

The application of statistical methods to medical data has been undergoing a sea-change. This is of particular importance in cardiology because the current methods that statisticians recommend express the results of studies in terms that are directly relevant to the clinical use to which they may be put. In March 1986 the *British Medical Journal* nailed its colours firmly to the mast, telling readers that "authors . . . will be expected to calculate confidence intervals whenever the data warrant this approach"^{1,2} and the *Lancet*,^{3,4} *Annals of Internal Medicine*, and *American Journal of Public Health* are among other journals that have endorsed the new orthodoxy. We expect that studies reported in the *British Heart Journal* will increasingly reflect this approach. The nuts and bolts of calculating the confidence intervals of various types of data are described in a series of articles in the *British Medical Journal*,⁵⁻⁹ and below we review some aspects of the approach that are particularly relevant to papers published in the *British Heart Journal*.

Towards estimation and away from hypothesis testing

The null hypothesis generally states that there is no relation between the variables under study. For example, when the change in cardiac output before and after intervention is analysed the null hypothesis proposes that the average change is zero. It follows that calculation of the p value, which is based on the null hypothesis, is frequently an inappropriate statistical method for summarising the analysis of cardiological data. Many published studies do not seriously consider the possibility that an intervention has no effect. When a test intervention has been used the question usually being asked is "how great is its effect?" rather than "does it have an effect?"

*Statistical adviser to the *British Heart Journal*.

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This point may be illustrated by comparing cardiac output before and after administration of an inotropic drug. A paired *t* test with a p value starts with the hypothesis that the inotrope has no effect. It is unlikely that the drug would be under investigation if no effect on cardiac output were really expected. The questions for the clinician are "on average, how great is the change produced by the intervention" and "with what precision has the average change been estimated?" These questions are answered by the calculation of confidence intervals, whereas hypothesis testing can give only the answer "yes" or "no" to the question "Is there a change?"

Figure 1a is an example of data that arise in such a study. The paired *t* test gives a value of $t = 3.3$ ($p = 0.01$). It indicates that the rise is statistically significant but does not indicate the size of the rise. The appropriate 95% confidence interval which is shown in fig 1a is based on the mean change and two standard errors on either side of the mean and suggests the likely interval within which the true mean lies. Thus the confidence interval centred on the mean change of 0.6 l/min extends from a mean change of +0.2 l/min to one of +1.0 l/min. This implies that the true mean value could lie anywhere between 0.2 and 1.0 and that the data are unlikely to be consistent with a mean change of zero. A confidence interval that does not include zero is equivalent to a test with a statistically significant p value. When the confidence interval includes zero, as for example when the interval is from -0.2 l/min to +1.4 l/min then although the mean change remains the same, at +0.6 l/min, the possibility must be considered that the intervention causes a fall rather than a rise or that it causes no change at all. If the data arise from a smaller sample (see fig 1b in which $n = 7$ instead of $n = 9$) or if their standard deviation is larger (see fig 1c in which the standard deviation has increased by 25%) the confidence interval will be wider.

When the confidence interval includes zero the

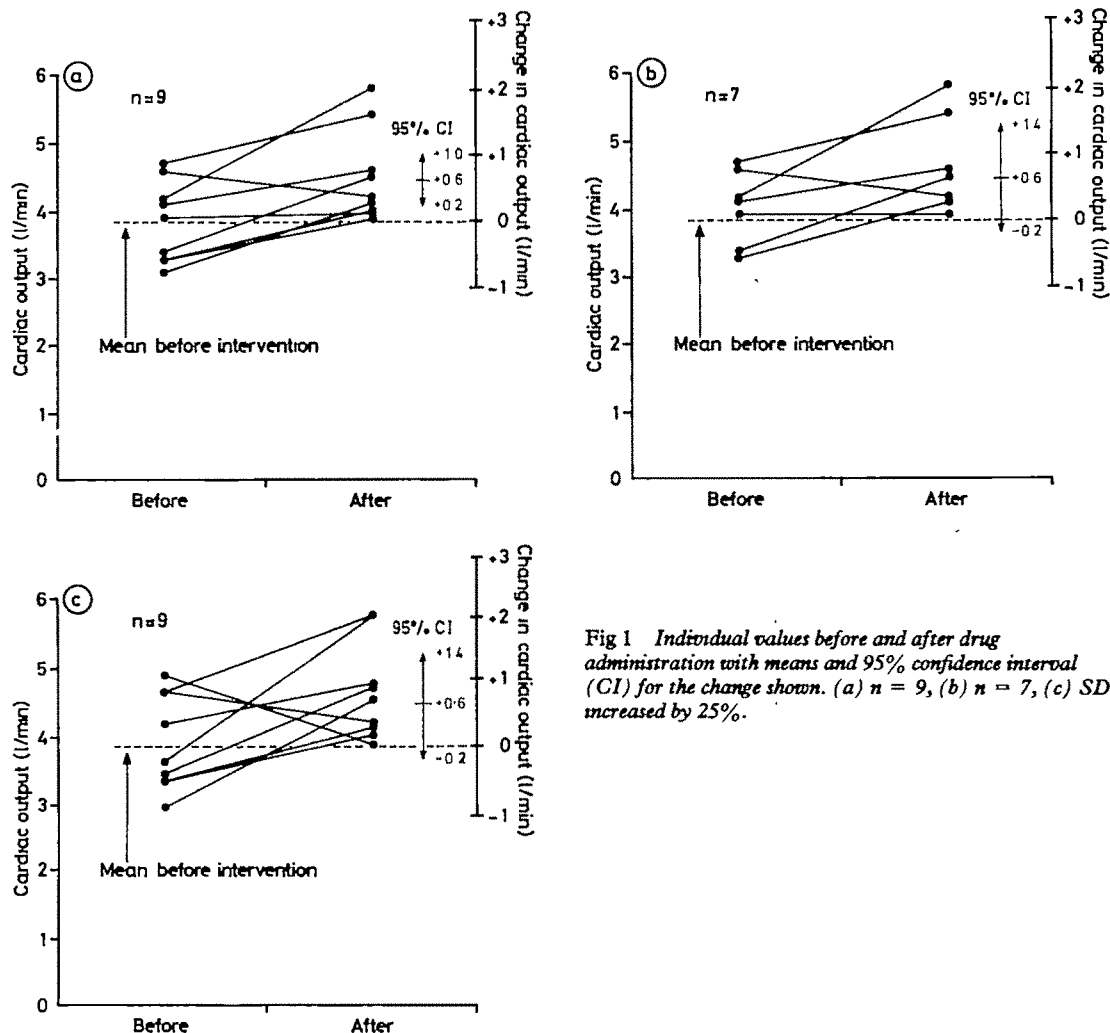


Fig 1 Individual values before and after drug administration with means and 95% confidence interval (CI) for the change shown. (a) $n = 9$, (b) $n = 7$, (c) SD increased by 25%.

result is equivalent to a significance test that gives a non-significant result. Relying on this feature alone is no better than the use of p values, but the upper limit of the confidence interval (+1.4) draws attention to the possibility that the average increase *might* be clinically useful.

The obvious advantage of a confidence interval is that it expresses results in the units in which the measurements were made, and so allows the reader to consider critically the clinical relevance of the results. If the sample size is small the confidence interval will be wide. The clinician must then examine the extremes of the interval. Do these extremes indicate that the clinical relevance of the results is consistent with the conclusions drawn from the analysis? If the conclusion is drawn that the drug has "no effect" because p is not statistically significant but the 95%

confidence interval reaches 1.4 l/min (fig 1b) then it is clear that the drug may well have a positive effect that has not been demonstrated by this study. The confidence interval (of say +0.05 to +0.1 l/min) can also make it clear that a difference which is statistically significant (based on p values) is of no clinical relevance because the statistical significance of the result has been produced spuriously by a very large sample of say about 2000. In such a study even the upper value of the confidence interval suggests that such a change is too small to be of clinical benefit despite its statistical significance.

When the effects of two different drugs on cardiac output are being compared the appropriate test is an independent samples t test and the equivalent 95% confidence interval may also be calculated. In fig 2, drug A gives the same results as shown in fig 1a, while

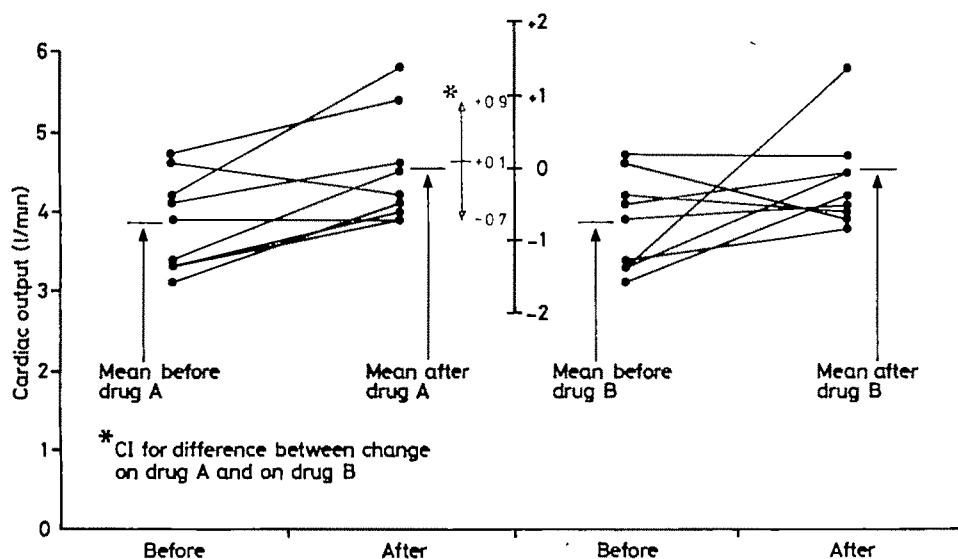


Fig 2 Individual and mean values before and after administration of two drugs. The 95% confidence interval for difference between the changes with drug A and the changes with drug B is -0.7 to $+0.9$ l/min.

the effect of drug B on cardiac output is "not statistically significant" when assessed by a paired *t* test. The relevant question is no longer simply whether each drug alters cardiac output but whether the change with drug A (δCO_A) is importantly

different from that with drug B (δCO_B). The 95% confidence interval for the difference between the changes with A and with B (δCO_{AB}) is -0.7 to $+0.9$ l/min. This shows that although the change with A is statistically significant ($p < 0.05$) and that with B is not statistically significant, there is insufficient evidence that the change with A is different from the change with B (because the 95% confidence interval for the difference in changes between A and B includes zero). At the same time confidence intervals show that potentially clinically important differences (for example of 0.9 l/min) between the drugs may not have been detected because the sample sizes were too small to produce significant *p* values.

Thus confidence intervals provide all the information that significance tests give us and also indicate the clinical relevance of the information. Confidence intervals require little more calculation than the appropriate significance test.

Method comparison and the null hypothesis

Many investigations in cardiology compare two methods of measuring the same variable—for example cardiac output determined by Doppler echocardiography and by the Fick principle at cardiac catheterisation. In the past, such data have been summarised by correlation or regression coefficients and calculation of a *p* value (fig 3a). In both these methods the null hypothesis is tested. But the null hypothesis, which states there is no association between two variables, is not relevant to the

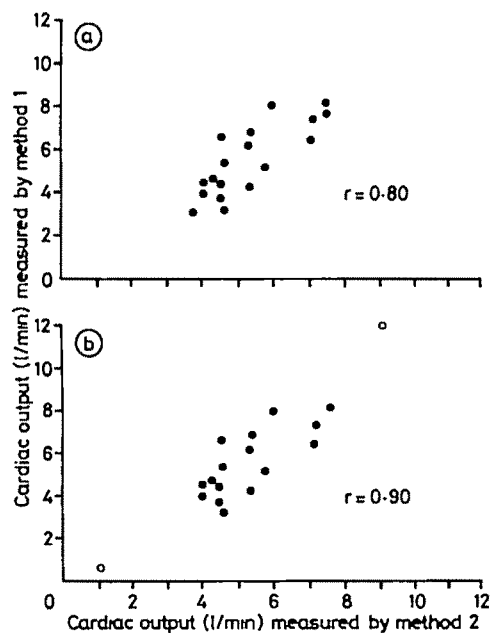


Fig 3 (a) Traditional scatter diagram for comparison of two methods of measuring cardiac output. (b) Two outlier values "improve" the correlation.

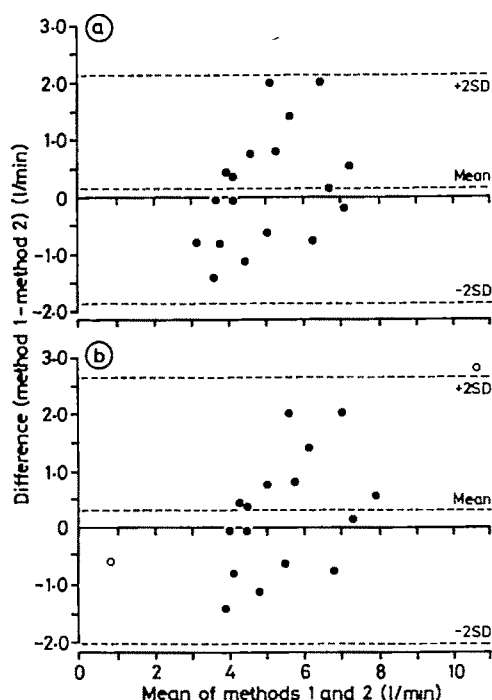


Fig 4 (a) Diagram showing differences versus mean for data in fig 3a. (b) The two outliers (circles) in fact produce a worse agreement between the methods.

measurement of the same variable by two different methods.¹⁰ The magnitude of the correlation coefficient is strongly influenced by the range of values under study. In addition, its "significance" is increased simply by increasing the number of subjects studied. The apparently stronger correlation between the variables for the data shown in fig 3b ($r = 0.90$ v $r = 0.80$) is purely the result of the inclusion of two outliers. The correlation coefficient gives neither the magnitude of any possible discrepancy between the two methods nor whether such discrepancy is consistent over the range of values.

Like confidence intervals the method of analysis advocated by Bland and Altman¹⁰ emphasises clinical relevance, which is determined by understanding the extent to which the two methods give different results—not by confirming that they show a little better than chance agreement when used to measure cardiac output. So fig 4a shows that method 1 gives slightly higher values than method 2 (the mean of the difference is higher than zero) and fig 4b shows that inclusion of the outlying values reduces the agreement rather than improves it (the standard deviation has increased from 1.00 to 1.17).

The key questions are what is the variability of a single observation (including its measurement error)

and how much disagreement is there between the two methods of measurement? It is also important to be aware of systematic variation in the answers over the range of interest; for example when the two sets of measurements are examined does one method yield high values at the upper end of the range and low values at the lower end of the range? If it does, are these discrepant values genuine or are they spurious? Investigation of the methods together with some understanding of the possible clinical applications will be necessary to decide which is the better method of measurement. Lastly, while the two methods may agree over a wide range of values including those of normal individuals, does this degree of agreement between the techniques extend into the range of values commonly encountered in disease?

For some time now the *British Heart Journal* has been informally persuading authors who inappropriately use correlation and regression coefficients to use the method of Bland and Altman to examine agreement between methods. The fact that, over many years, correlation and regression have been misused is no reason to perpetuate a bad practice. Comparison of the r values obtained in different studies is meaningless. In addition, the *British Heart Journal* also recommends that confidence intervals should be given where relevant for studies that assess the effects of interventions, compare the effects of different drugs, or evaluate non-invasive techniques.

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High gain signal averaged electrocardiogram combined with 24 hour monitoring in patients early after myocardial infarction for bedside prediction of arrhythmic events

T CRIPPS,* E D BENNETT,† A J CAMM,* D E WARD*

From the Departments of *Cardiological Sciences and †Medicine I, St George's Hospital Medical School, London

SUMMARY The value of the high gain, signal averaged electrocardiogram combined with 24 hour electrocardiographic monitoring in the prediction of arrhythmic events was assessed in 159 patients in the first week after myocardial infarction. Eleven patients (7%) suffered arrhythmic events during a mean (SD) of 12 (6) months of follow up (range 2-22, median 13 months). The combination of high gain, signal averaged electrocardiography and 24 hour electrocardiographic monitoring was more accurate than either technique alone or than clinical information collected during admission in predicting these events. The combination identified a high risk group of 13 (8%) patients, with an arrhythmic event rate of 62% and a low risk group with an event rate of 2%.

The combination of high gain, signal averaged electrocardiography and 24 hour electrocardiographic monitoring in the first week after myocardial infarction provides a rapid, cheap, and non-invasive bedside method for the prediction of arrhythmias.

The assessment of prognosis after myocardial infarction is of potential value, both to those judged to be at low risk, who can be reassured and spared further investigation and treatment, and to those at high risk, upon whom diagnostic and therapeutic facilities can be focused. An assessment of any tendency to cardiac arrhythmias is especially important in patients after myocardial infarction since ventricular arrhythmias have been strongly implicated as an important cause of sudden death in this group.^{1,2} Recently it has been shown that areas of late myocardial depolarisation, which may be a basis for re-entry, can be detected at the body surface by a high gain signal averaged electrocardiogram.³

As with 24 hour electrocardiographic monitoring, however, the predictive accuracy of the signal averaged electrocardiogram is low, limiting its clinical usefulness. A combination of signal averaged

electrocardiography and 24 hour electrocardiographic monitoring increased the accuracy of arrhythmia prediction.^{4,5} We have therefore carried out a prospective study of a population of consecutive patients with myocardial infarction to confirm and extend these observations. In this study we also considered the value of signal averaged electrocardiogram recordings obtained within the first 72 hours after infarction.

Patients and methods

All patients of ≤ 70 admitted to the hospital between 1 May 1986 and 1 December 1987 as general medical emergencies having sustained a myocardial infarction within the previous 24 hours were seen within 48 hours of admission and considered for inclusion in the study, which was approved by the regional ethics committee. Myocardial infarction was diagnosed when two or more of the following features were present: (a) chest pain suggestive of myocardial ischaemia persisting for at least 20 minutes and unrelieved by glyceryl trinitrate; (b) sequential rise and fall in the plasma concentrations of aspartate

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transaminase, 2-hydroxybutyrate dehydrogenase, and/or creatine kinase with a peak concentration of at least twice the upper limit of the reference range for our laboratory; (c) development of new abnormal Q waves, or persistent ST/T changes suggestive of non-Q wave myocardial infarction. Patients were excluded if they had non-cardiac disease likely to influence mortality, important non-ischaemic cardiac disease, a history of previous cardiac surgery or permanent pacemaker insertion, if they had atrial fibrillation or bundle branch block, if they refused or were unable to attend for follow up. Since this was a long term prognostic study, we also excluded patients who died or had operation within seven days after the onset of myocardial infarction, the usual time of hospital discharge. To ensure that the population studied would be representative of patients admitted to a general hospital with myocardial infarction we excluded patients transferred from other hospitals to the regional cardiothoracic unit. Those with previous infarction were included, as were those with both Q and non-Q wave infarction.

CLINICAL ASSESSMENT

TC obtained a history and carried out a physical examination in all cases as soon as possible after admission. The 12 lead electrocardiogram and chest radiograph were reviewed and the Killip class⁶ and Norris index⁷ were determined. Blood was sent for measurement of cardiac enzymes, and a 12 lead electrocardiogram was recorded on admission and on the morning of the first three days after admission. Patients were monitored on the intensive care unit for the first 24-48 hours or as clinical circumstances dictated and early arrhythmias were recorded by a central monitoring system. During admission patients were reviewed daily and the occurrence of in-hospital complications was noted.

SIGNAL AVERAGED ELECTROCARDIOGRAM

A high gain, signal averaged electrocardiogram was obtained during admission with a commercially available system (Model 101 electrocardiograph, Arrhythmia Research Technology, Oklahoma, USA). This system uses the method developed by Simson for the detection of late potentials and has been described in detail elsewhere.⁸ Briefly, after preparation of the skin with an alcohol swab and careful abrasion, pre-gelled electrodes were applied in the Frank orthogonal lead configuration and the surface electrocardiogram was amplified by a factor of 5000, digitised, filtered low-pass at 250 Hz and high-pass at 25 Hz (with bidirectional filters to eliminate ringing), and 200-500 beats were averaged to achieve a noise level of $< 1.0 \mu\text{V}$. A vector magnitude display (the filtered QRS complex) was

generated, and the late potentials were defined as the presence of one or more of: (a) filtered QRS duration (fQRSd) of ≥ 120 ms; (b) duration of the filtered QRS complex after voltage falls below $40 \mu\text{V}$ (LPD40) of ≥ 40 ms, and (c) root mean square voltage during the last 40 ms of the filtered QRS complex (RMSV40) of $\leq 25 \mu\text{V}$. The signal averaged electrocardiogram was obtained at the bedside within 5-10 minutes.

Reproducibility was assessed in 20 patients selected at random at one month after myocardial infarction. Consecutive recordings were made without any technical or environmental changes, both recordings being completed within 15 minutes. The noise level achieved in the two recordings was the same, to within $\pm 0.1 \mu\text{V}$ in each subject. Changes in the signal averaged electrocardiographic variables were assessed in 58 patients who had an initial recording within 72 hours of the onset of symptoms and a second recording at the first outpatient follow up visit.

24 HOUR MONITORING

The electrocardiogram was monitored for 24 hours > 6 days after myocardial infarction on a Tracker recorder (Reynolds Medical Ltd., Hertford, England). Leads CM5 and modified lead III were recorded. We used a semiautomated system to analyse the 24 hour electrocardiograms for arrhythmias (Pathfinder III system, Reynolds Medical Ltd., Hertford). The frequency of ventricular extrasystoles over the 24 hour period was calculated and the occurrence of multiform extrasystoles, couplets, and ventricular tachycardia (a run of three or more ventricular extrasystoles) was noted. In no case was the occurrence of asymptomatic arrhythmias on 24 hour monitoring considered to be an arrhythmic event.

FOLLOW UP

Patients were seen at 1, 3, 6, and 12 months, or as clinical circumstances dictated. We telephoned the patient's general practitioner and relatives if a patient did not attend for a clinic appointment to find out whether the patient had died, and if so how. Sudden cardiac death was defined as witnessed sudden death in or out of hospital not preceded by chest pain. Sustained ventricular tachycardia was defined as documented ventricular tachycardia lasting for 30 seconds or associated with symptomatic hypotension. An arrhythmic event was defined as either sudden cardiac death or the occurrence of sustained ventricular tachycardia. In all cases the arrhythmic events occurred after completion of the signal averaged electrocardiogram and 24 hour tape.

Results

PATIENT POPULATION

During the period of this study, May 1986 to December 1987, 232 patients under the age of 71 were admitted to the hospital as general medical emergencies with proven myocardial infarction and without other life threatening disease. After exclusion because of death (22) or cardiac surgery (4) within seven days of infarction, previous cardiac surgery (6), refusal or inability to attend follow up (9), bundle branch block (7), atrial fibrillation (2), technical problems with the 24 hour electrocardiogram (13), and administrative problems (10), 159 patients remained who had both signal averaged electrocardiography and 24 hour electrocardiography. The mean (SD) age of this group was 56 (9) years (range 28–70). Twenty per cent were female; there was a history of previous infarction in 14%. Q wave infarction was present in 67% and non-Q wave infarction in 33%. The Killip class on admission was I in 88%, II in 8%, III in 3%, and IV in 1%; the Norris index was > 10 in 7%.

HIGH GAIN, SIGNAL AVERAGED ELECTROCARDIOGRAPHY

The initial signal averaged electrocardiogram recording was made (mean (SD)) 3(2) days (range 0–10, median 3) after infarction. A late potential, as defined above, was present in 38/159 (24%) of patients. In the reproducibility study, the standard deviation of the differences between the first and second recordings was 4 ms for fQRS, 2.9 ms for LPD40, and 6.1 ms for RMSV40. The range within which a single measurement could be reproduced (with 95% probability) on a second occasion was thus ± 8 ms for fQRS, ± 6 ms for LDP40, and ± 12 μ V for RMSV40. Of those 58 patients in whom an initial recording was made < 72 hours after infarction and repeated at follow up, nine (82%) of 11 patients had late potentials at both recordings, and five of these had arrhythmic events (one sudden cardiac death and four ventricular tachycardia). Of those 47 patients

with an early initial recording without late potentials, only two (4%) had them at follow up; neither of these patients had an arrhythmic event. All of these changes were outside the 95% confidence intervals. There was no significant change in the mean values of the signal averaged electrocardiogram variables between recordings obtained within the first 72 hours and at follow up.

TWENTY FOUR HOUR ELECTROCARDIOGRAPHIC MONITORING

Twenty four hour electrocardiograms were recorded > 6 days after infarction in all patients. In 30 patients there were > 10 ventricular extrasystoles per hour. Ventricular tachycardia (three or more consecutive beats) were recorded in 12 patients.

FOLLOW UP

No patient was lost to follow up. During follow up of (mean (SD)) 12(6) months (range 2–16) seven patients died, five of them in circumstances suggesting a primarily arrhythmic death, and six had documented sustained symptomatic ventricular tachycardia occurring more than 48 hours after myocardial infarction. Thus there were 11 (7%) patients who had an arrhythmic event. Table 1 shows the sensitivity, specificity, and positive predictive value of the high gain signal averaged electrocardiogram and of 24 hour electrocardiographic monitoring in predicting these events. It is clear that on their own both 24 hour tape and signal averaged electrocardiogram were fairly sensitive in predicting arrhythmic events but had low positive predictive accuracy (27% for 24 hour tape and 26% for late potentials). When both tests were positive the positive predictive accuracy for predicting arrhythmic events was, however, much higher (62%) yet the sensitivity of the combination was retained (73%). All but one of the patients with positive results in both tests but no arrhythmic events had undergone coronary artery bypass surgery, which may have influenced the outcome.

Table 1 also shows the value of the clinical findings

Table 1 Value (%) of ambulatory monitoring and signal averaged electrocardiography in predicting risk of arrhythmic events

	Sensitivity	Specificity	PPA	Efficiency
Killip class $\geq$ II	6/11 (55)	135/148 (91)	6/19 (32)	141/159 (89)
Norris index $>$ 9	5/11 (45)	141/148 (95)	5/12 (42)	146/159 (92)
Signal averaged ECG (LP+)	10/11 (91)	120/148 (81)	10/38 (26)	130/159 (82)
24 hour tape (FVE $\geq$ 10/hour)	8/11 (73)	126/148 (85)	8/30 (27)	134/159 (84)
Both tape and Killip class $\geq$ II	4/11 (36)	144/148 (97)	4/8 (50)	148/159 (93)
Both LP+ and Killip class $\geq$ II	5/11 (45)	145/148 (98)	5/8 (63)	150/159 (94)
Both LP+ and FVE $\geq$ 10/hour	8/11 (73)	143/148 (97)	8/13 (62)	151/159 (97)

PPA, positive predictive accuracy; LP+, late potentials present; FVE, frequency of ventricular extrasystoles.

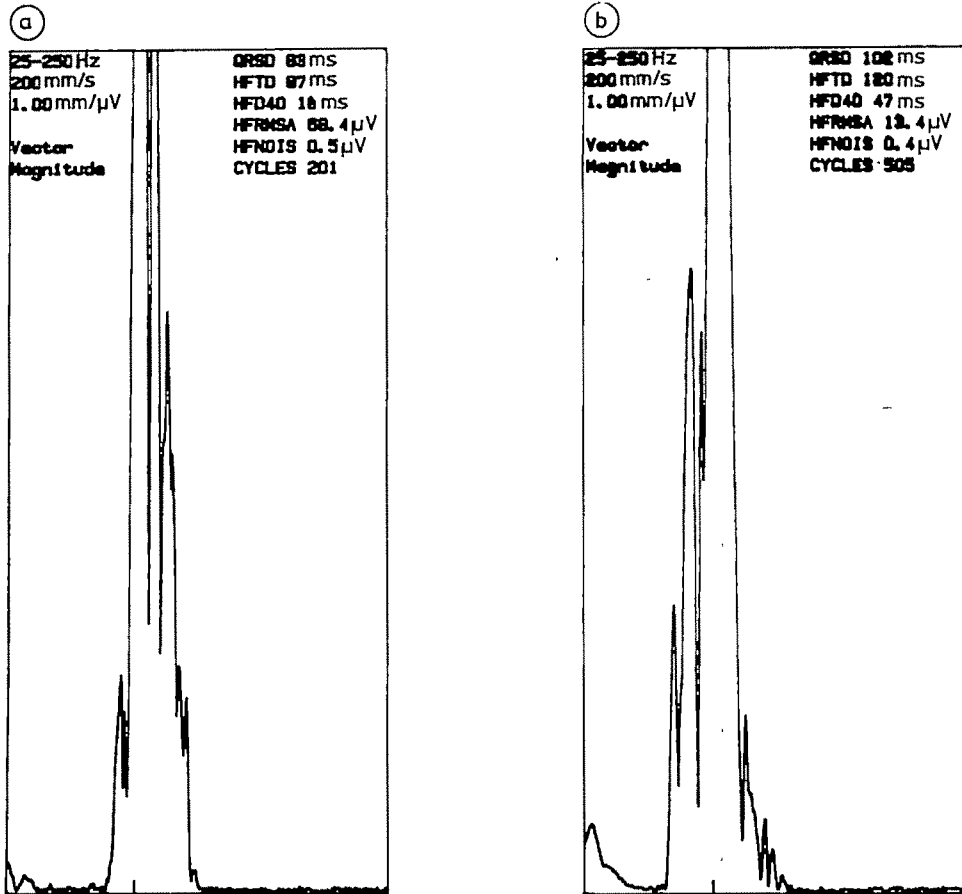


Figure An example of two high gain signal averaged electrocardiograms. (a) This recording is within normal limits and was recorded from a patient with an uncomplicated course. (b) This recording comes from a patient who died suddenly after myocardial infarction and it shows a prominent late potential. QRS_D, QRS duration; HFTD, high frequency total QRS duration; HFD40, duration of high frequency low amplitude signals ($< 40 \mu$ V); HFRMSA, high frequency root mean square voltage of signals in the last 40 ms of the high frequency QRS; HFNOIS, high frequency noise level; cycles, number of averaged QRS complexes.

on admission (Killip class and Norris index) in predicting arrhythmic events. Clinical evidence of substantial infarction (that is Killip class $\geq$ II or a Norris index of > 9) was specific for the prediction of arrhythmic events (specificity 91% and 95% respectively), but was insensitive (sensitivities 55% and 45%). Thus the value of a combination of either a positive tape (≥ 10 ventricular extrasystoles/hour) or late potentials with the clinical data was limited by low sensitivity (sensitivity 36% for tape with Killip $\geq$ II and 45% for late potentials with Killip $\geq$ II), though the positive predictive value of each test was improved by taking into account the Killip class (positive predictive accuracy 50% for tape in the

presence of Killip class $\geq$ II and 63% for late potentials in the presence of Killip class $\geq$ II).

Discussion

The purpose of this study was to confirm that in the first week after myocardial infarction two bedside non-invasive techniques (signal averaged electrocardiography and 24 hour electrocardiographic monitoring) give an accurate assessment of the risk of the occurrence of sudden death and sustained ventricular tachycardia. Previous studies have established the relation between prognosis after myocardial infarction and the results of 24 hour electrocar-

Table 2 Prospective large scale studies of the value of signal averaged electrocardiography and ambulatory monitoring in the prediction of arrhythmic events after acute myocardial infarction

Authors	No	Mean (SD) time since MI (h)	SAECG	Filter	Criteria for positive SAECG				Prediction of AE		
					fQRS	LPD40	RMSV40	Noise	Sens	Spec	PPA
Kuchar <i>et al.</i> ⁴	200	11(6)	ART	40 Hz	> 120	—	< 20	n/s	65	89	32
Gomes <i>et al.</i> ⁵	102	10(6)	ART	40 Hz	> 114	> 38	< 20	n/s	100	45	35
Present study	159	3(3)	ART	25 Hz	≥ 120	> 40	≤ 25	< 1μV	73	97	62

No, number of patients having both signal averaged ECG and 24 hour tape; SAECG, high gain, signal averaged electrocardiogram; sens, sensitivity; spec, specificity; PPA, positive predictive accuracy, n/s, not stated; AE, arrhythmic events; fQRS, filtered QRS duration of ≥ 120 ms; LPD40, duration of the filtered QRS complex after voltage falls below $40 \mu\text{V}$ of ≥ 40 ms; RMSV40, root mean square voltage during the last 40 ms of the filtered QRS complex of $\leq 25 \mu\text{V}$; ART, Arrhythmia Research Technology.

diographic monitoring⁹⁻¹¹ and the high gain, signal averaged electrocardiogram. Although both tests provide prognostic information that is independent of clinical assessment and ejection fraction their clinical usefulness is limited by their low positive predictive accuracy.

Others have examined the relation between the results of signal averaged electrocardiogram and 24 hour electrocardiographic monitoring. The study of Kanovsky *et al.* was not prospective nor did they evaluate consecutive series of patients with myocardial infarction.¹² They compared two groups of patients referred for invasive investigation—a control group that did not have a history of ventricular tachycardia at a median of eight weeks after myocardial infarction and a group with documented ventricular tachycardia at a median of 46 weeks after infarction. No follow up data on the “control” group was available and so in some of them arrhythmic events could have developed subsequently. The presence of a late potential (fQRS > 120 ms and/or RMSV40 $< 25 \mu\text{V}$), the presence on 24 hour monitoring of a peak rate for ventricular extrasystoles of > 100 per hour, and the presence of an aneurysm on cineventriculography were independently associated with a history of ventricular tachycardia. There was little improvement in the prediction of arrhythmic events when the results of signal averaged electrocardiography were combined with either those of 24 hour monitoring or contrast ventriculography, but when all three were combined a sensitivity of 81%, a specificity of 90%, and a predictive accuracy of 85% were achieved.

More recently, Kuchar *et al.*⁴ reported a study that was similar in design to our own. They too found an independent association between the results of signal averaged electrocardiography, 24 hour monitoring (Lown grade), and left ventricular function assessed by radionuclide angiography. The power of the combination of signal averaged electrocardiogram and 24 hour electrocardiographic monitoring in the prediction of arrhythmic events was: sensitivity 65%, specificity 89%, and positive predictive

accuracy 32%. A second series has been reported by Gomes *et al.*⁵ Again the triad of ejection fraction, signal averaged electrocardiogram, and 24 hour electrocardiographic monitoring was assessed in relation to arrhythmic events during follow up, by the system used by Kuchar *et al.* Table 2 shows that the accuracy of prediction of arrhythmic events was more sensitive but less specific than that reported by Kuchar *et al.* A further increase in predictive accuracy, from 35% to 50%, was achieved, without loss of sensitivity, by adding ejection fraction data.

In accord with the previous studies we found that the signal averaged electrocardiogram, while acceptably sensitive in predicting arrhythmic events during follow up after myocardial infarction (91%), had a low positive predictive accuracy (26%), which limits its clinical usefulness. In combination with the 24 hour tape, however, the predictive accuracy is increased considerably, with only moderate loss of sensitivity (table 2). Of the five patients who had positive results in both tests but have not yet had an arrhythmic event, three have had coronary artery bypass surgery which will have influenced the outcome. Longer follow up may increase the accuracy of this predictive combination even further.

It is not certain why the predictive accuracy of the combination of tape and signal averaged electrocardiogram was higher in our study than it was in those of Kuchar *et al.* and Gomes *et al.* There were, however, several differences in the three studies. In our study the signal averaged electrocardiogram was performed earlier than in the other two studies, in most cases within the first week and in 44 (28%) cases within the first day after infarction. It is often assumed that, in view of the evidence that there is variability in some of the electrophysiological properties of the myocardium soon after infarction,¹³ the signal averaged electrocardiogram will also be labile if recorded soon after infarction. This has not been our experience: there were no more changes between < 72 hours and one month follow up than was reported for a > 1 month and 6 month follow up,¹⁴ and comparable prognostic information was

obtained from these early recordings. Many physicians discharge patients a week or even earlier after myocardial infarction and if information on the tendency to arrhythmia can be obtained before discharge it will be useful in management. Furthermore, some patients who die of early arrhythmia may be missed without early analysis. The population we studied may have differed in some respects from those in previous studies, none of which were from the United Kingdom. Our population consisted of a consecutive series of patients admitted with acute myocardial infarction and was representative of patients admitted to a general hospital with acute myocardial infarction.

Another important difference between the studies is the corner frequency chosen for high pass filtering of the signal averaged electrocardiogram. The equipment we used resembles that of Kuchar *et al.*⁴ and Gomes *et al.*⁵ except that the high pass filter was fixed at 25 Hz rather than 40 Hz. The optimal level for filtering is not known: the system of Breithardt *et al.*¹⁵ uses a high pass filter at 100 Hz, that of Uther's group uses virtually no filtering at all.¹⁶ Gomes *et al.*¹⁷ subsequently found that the 25 Hz filter had less sensitivity but more specificity than the 40 Hz filter in identifying patients with a history of ventricular tachycardia and those without. This is entirely consistent with our results (table 2).

The values used for the definition of the presence of late potentials is also different in the three studies (table 2). Our groups were selected before the start of the study and were based on Simson's comparison of patients with a history of myocardial infarction with or without documented ventricular tachycardia in which he used a comparable system with 25 Hz filtering.⁸ We also used the frequency of extrasystoles rather than Lown grade to quantify the arrhythmias on 24 hour electrocardiographic monitoring, as did Kuchar *et al.*⁴ because the Lown system has some deficiencies,¹⁸ particularly the undue weight given to early extrasystoles (Lown grade 5).

We did not examine in detail the relation between left ventricular function and arrhythmic events. Although several studies have shown the importance of left ventricular ejection fraction as a prognostic determinant, accurate objective measurement of left ventricular function is not widely available. Most district hospitals do not have access to radionuclide ventriculography, and it is neither desirable nor possible to refer all patients with myocardial infarction for cineangiographic ventriculography. Access to 24 hour electrocardiographic monitoring, however, is more general, and has the great advantage that it can be performed by a technician. The signal averaged electrocardiograph we used is simple to use. At present it is little used, but if it were shown to be of

clinical value it could be installed at a fraction of the cost of the equipment and expertise required for radionuclide angiography. We suggest that simple, rapid, cheap non-invasive tests should be used in the first instance to screen post-infarction patients, who then may proceed to more detailed evaluation if the screening tests are positive.

We did not include the results of exercise testing, which has an established place in risk stratification after myocardial infarction, in this study. This test would be expected to be of particular value in predicting ischaemic events after infarction and is therefore complementary to the tests we have described, which are directed purely to the identification of arrhythmic risk. We used only arrhythmic events as end points in this study.

We have, however, examined the clinical state of the patients on admission, as reflected in the Killip class and Norris index, to determine whether the predictive value of the signal averaged electrocardiogram and 24 hour monitoring was equalled or even exceeded by simple clinical observation. Although the clinical state of the patient on admission did have some value in predicting outcome, the sensitivity and predictive value were less than either of the tests individually, and considerably less than those of the combination. Clinical variables are designed to be prognostic of in-hospital mortality, and those who died in the first seven days were excluded from our long term prognostic study.

As expected, the positive predictive accuracy of both the tape and the signal averaged electrocardiogram was greater if there was also clinical evidence of substantial infarction, but the value of these combinations in predicting arrhythmic events was limited by their lower sensitivity. Thus while the positive predictive accuracy of a positive tape (≥ 10 ventricular extrasystoles per hour) in a patient with Killip class $\geq II$ was increased to 50%, this finding was present in only four of 11 patients with arrhythmic events. With the combination of a positive tape and late potentials the sensitivity remained fairly high (8/11 arrhythmic events predicted), and there was a substantial increase in positive predictive accuracy (8/13 with positive results had an event). Our results suggest that the tendency to arrhythmia can be accurately assessed within the first week of myocardial infarction by a combination of the high gain, signal averaged electrocardiogram and 24 hour electrocardiographic monitoring. The value of antiarrhythmic treatment in this high risk group is uncertain, but the identification of a group of patients with a very high risk of arrhythmic events will increase the power of trials designed to test the value of antiarrhythmic treatment in patients after myocardial infarction.

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Left ventricular volume measured rapidly by oblique magnetic resonance imaging

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SUMMARY Magnetic resonance measurements of left ventricular volume and ejection fraction based on measurements of area and length in a single oblique plane containing the long axis of the ventricle were compared with measurements made by summing the areas of the chamber in multiple contiguous slices. The multislice technique is known to be accurate, but the single slice technique is much quicker; it takes only nine minutes of acquisition time for both volume and ejection fraction. In 25 normal subjects there was good agreement between the two methods of measuring volume with a mean (SD) difference between measurements of 2.0 (6.6) ml. In 20 patients with previous infarction it was less good with a mean (SD) difference of 4.5 (18.1) ml. The mean (SD) difference of ejection fraction measurements was -0.019 (0.038) in the normal subjects and -0.059 (0.106) in the patients, and the discrepancy between the two techniques was greatest in the patients with a pronounced abnormality of wall motion and low ejection fraction. In a further 25 normal subjects, the agreement between single plane volume measurements in the vertical and horizontal long axis planes was good, indicating that either plane is suitable for rapid measurement.

Single plane measurements of left ventricular volume and ejection fraction can be made with the accuracies stated, which are sufficient for routine clinical use except in patients with a pronounced abnormality of wall motion. In combination with measurements of regional wall thickness and motion, previously described, the technique offers a rapid non-invasive assessment of both global and regional left ventricular function.

Left ventricular volume and ejection fraction are widely used as measures of global function. We have previously shown that magnetic resonance imaging provides an accurate method of measuring volume by summing the areas of the ventricle in contiguous transverse slices,¹ and that these measurements have clinical value in the determination of global ventricular function and regurgitant fraction.² Eight acquisitions are usually required to cover the whole left ventricle, however, and this may take up to 40 minutes, depending upon heart rate. Because images can now be acquired in oblique planes, more rapid measurements can be made from images containing the long axis of the left ventricle if the ventricle is assumed to be an ellipsoid of revolution about the long axis. Volume can then be calculated from a

single image and ejection fraction from a pair of images at end diastole and end systole.

To assess the validity of the rapid technique for routine use we compared measurements of left ventricular volume and ejection fraction from oblique images with those made by the multislice technique.

Patients and methods

We studied 50 symptom free volunteers without a history of cardiac disease (mean age 42, range 25-64), subsequently referred to as "normal subjects" because they were assumed to have normal left ventricular function. We also studied 20 patients with previous myocardial infarction (mean age 51, range 40-73), which was established on the basis of the history and the electrocardiogram in conjunction with regional abnormalities of left ventricular contraction seen by either right anterior oblique x ray contrast ventriculography or left anterior oblique

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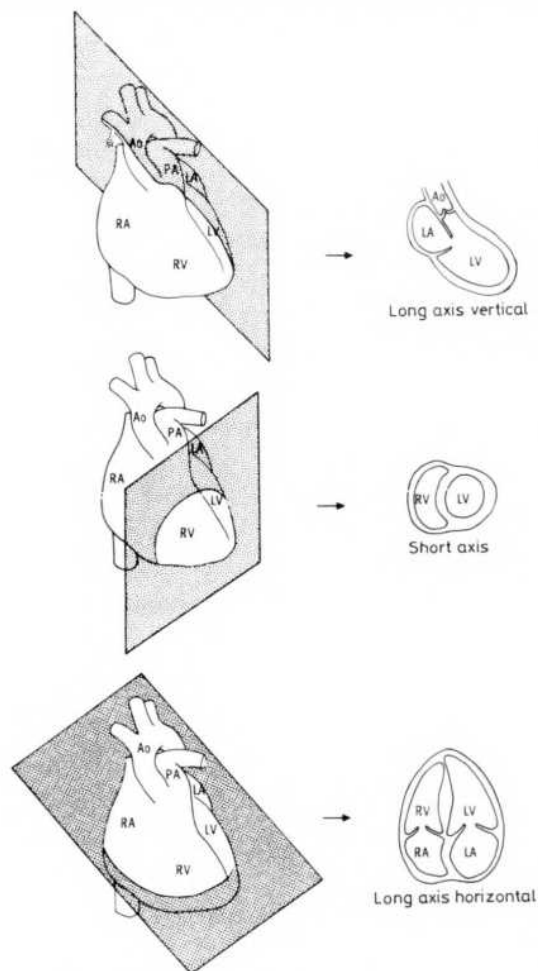


Fig 1 The vertical and horizontal long axis planes contain the long axis of the left ventricle and are roughly equivalent to the right anterior oblique view in x ray contrast ventriculography and the apical four chamber view of echocardiography respectively.

equilibrium radionuclide ventriculography. The site of infarction was judged from the ventriculograms and there were abnormalities of the anterior wall in 14 patients, the septum in six, the inferior wall in nine, the lateral wall in two, and the apex in nine.

In the patients with previous infarction and in 25 of the normal subjects, volumes were measured by magnetic resonance by both the multislice method and a single plane area-length method in the horizontal long axis plane (fig 1). Radionuclide ventriculography was performed only in the patients and the radionuclide left ventricular ejection fraction was compared with the multislice magnetic resonance technique. The other 25 normal subjects were

studied at a later date, when software improvements allowed both vertical and horizontal long axis planes to be imaged. In these subjects, we compared single plane area-length measurements in the horizontal and the vertical long axis planes and biplane measurements in which both planes were used.

We used a Picker International Vista MR2055 scanner operating at 0.5 tesla and an electrocardiographically gated spin echo sequence with an echo time of 40 ms. Each acquisition consisted of two averages of 128 phase encoding steps; the pixel size was $1.17 \text{ mm} \times 1.17 \text{ mm}$ and the slice thickness was 10 mm. In the initial study of 25 normal subjects and 20 patients with infarcts, measurements were made in the horizontal long axis plane, and the angle of depression of the long axis was determined from an initial sagittal image through the body of the left ventricle. In this plane, contiguous slices were acquired at end diastole and end systole to cover the whole left ventricle and the images were acquired in

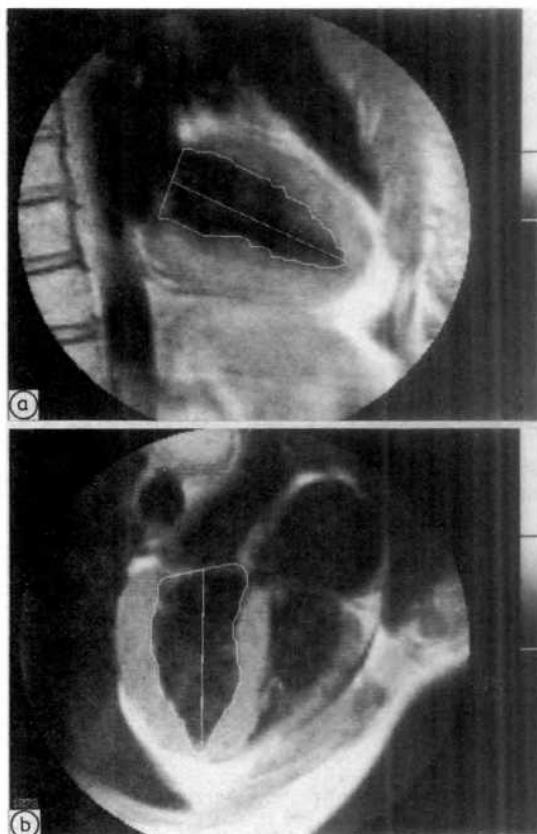


Fig 2 The area and length of the left ventricle in vertical (a) and horizontal long axis planes (b) were measured by tracing on the computer screen. The images displayed are of a normal subject with an end diastolic volume of 125 ml.

pairs—diastole at one level and systole in another. The end systolic image was timed to coincide with the end of the electrocardiographic T wave. Total acquisition time was approximately 30 minutes depending upon heart rate, but if the horizontal long axis images alone had been acquired it would have been five minutes for a single volume measurement or nine minutes for an ejection fraction measurement.

In the subsequent study of a further 25 normal subjects, the horizontal and vertical long axis planes were used (fig 2). An initial transverse image was acquired through the body of the left ventricle, and from this, the rotation of the ventricle towards the left could be seen. The vertical long axis images were acquired perpendicularly to the transverse plane but they were rotated to include the long axis of the ventricle. The depression of the ventricle was seen from the vertical long axis image and this permitted the horizontal long axis plane to be acquired.

Left ventricular endocardial contours were drawn manually on the computer screen and volume was calculated either by summing the area of the contour in each image (multislice technique) or from the central images containing the long axis of the ventricle (area-length technique). The following formulas were used for the area-length calculations³:

$$\text{Single plane } V = (8 \times A^2) / (3\pi \times L)$$

$$\text{Biplane } V = (8 \times A_v \times A_h) / (3\pi \times L_{\min})$$

where A represents the area of the left ventricular cavity, L the distance from apical endocardium to

mitral valve plane, the v and h subscripts refer to vertical and horizontal lung axis planes, and the min subscript to whichever value of L is smaller (fig 2).

Equilibrium radionuclide ventriculography was performed in a left anterior oblique projection with 30° of caudal tilt after labelling the erythrocytes with 740 MBq of technetium-99m sodium pertechnetate. Sixteen frames per cardiac cycle were acquired and left ventricular ejection fraction was calculated from counts within a left ventricular region of interest after functional background subtraction.⁴ First harmonic Fourier amplitude and phase images were used to detect regional wall motion abnormalities.⁵

Volume and ejection fraction measurements were compared by the methods outlined by Bland and Altman.⁶ Probability was assessed by Student's *t* test.

Results

Figure 3 compares the multislice measurements of left ventricular volume and the single plane area-length measurements in the first 25 normal subjects. Figure 3a shows the individual data points and fig 3b plots the difference between measurements against the mean of the two measurements. The table shows the statistics derived from these data and from the data in all subsequent figures. The mean difference between measurements did not differ significantly from zero at end diastole ($p > 0.1$), but at end systole the mean difference was 2.7 ml which was significantly greater than zero ($p < 0.01$), indicating that the area-length measurements were slightly under-

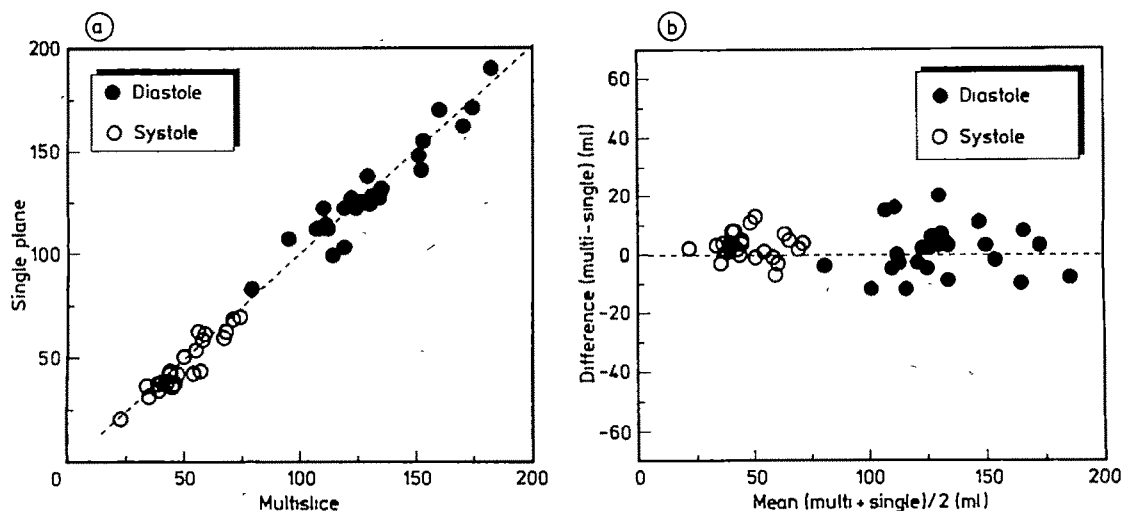


Fig 3 (a) Individual data points for single plane area-length measurements of left ventricular volume and multislice measurements in 25 normal subjects. The dotted line is the line of identity. (b) Difference between measurements plotted against the mean of each pair of measurements.

Table Data derived from single and multislice magnetic resonance imaging

Comparison	Subjects	No	Mean	Mean diff	SD diff	Error	p
Single v multi volume (ml)	Normal						
Diastole		25	131	1.3	8.2	6.2%	NS
Systole		25	51	2.7	4.5	8.8%	<0.01
Combined		50	92	2.0	6.7	7.3%	<0.05
Single v multi volume (ml)	Infarct						
Diastole		20	187	-1.1	17.8	9.6%	NS
Systole		20	114	10.1	18.4	16.1%	<0.01
Combined		40	150	4.5	19.0	12.6%	NS
Single v multi EF	Normal	25	0.62	-0.019	0.038	6.2%	<0.01
Single v multi EF	Infarct	20	0.41	-0.059	0.106	25.7%	<0.01
Single (VLA) v biplane (ml)	Normal	50	87	-2.2	12.2	14.1%	<0.05
Single (HLA) v biplane (ml)	Normal	50	87	-5.0	12.2	14.1%	<0.05
Single (VLA) v single (HLA)	Normal	50	90	2.8	23.1	25.6%	NS
Radionuclide v multi EF	Infarct	20	0.41	0.026	0.052	12.5%	<0.001

No, number of measurements; mean, mean of the measurements; mean diff, mean difference between measurements (the second minus the first); SD diff, standard deviation of the difference between measurements; error, SD diff - mean, single, single plane area length measurement; biplane, biplane area length measurement; multi, multislice measurement; VLA, vertical long axis; HLA, horizontal long axis; EF, ejection fraction

estimated. The standard deviation of the difference between measurements (SD diff) and the percentage error ((SD diff)/mean) were sufficiently low (8.2 ml (6.2%) diastole, 4.5 ml (8.8%) systole) for the area-length measurements to be clinically useful in normal subjects.

Figure 4 compares the volume measurements in the 20 patients with previous infarction. As in the normal subjects, the mean difference between measurements did not differ significantly from zero at end diastole ($p > 0.5$), but at end systole the area-length technique gave a slight underestimate of volume (mean difference 10.1 ml, $p < 0.05$). The standard deviation of the difference between

measurements and the percentage error, however, were much higher than in the normal subjects (17.8 ml (9.6%) diastole, 18.4 ml (16.1%) systole). There was no obvious difference between those with anterior or septal infarction and those with inferior infarction. Figure 5 shows the systolic horizontal long axis image of a patient with anterolateral infarction and apical dyskinesia. The shape of the left ventricle was irregular compared with the normal subject in fig 2 and there is thinning of the lateral wall with considerable thinning at the apex. The multislice measurements of diastolic and systolic volume were 195 ml and 125 ml, giving an ejection fraction of 0.37, and the area-length volumes were 180 ml and

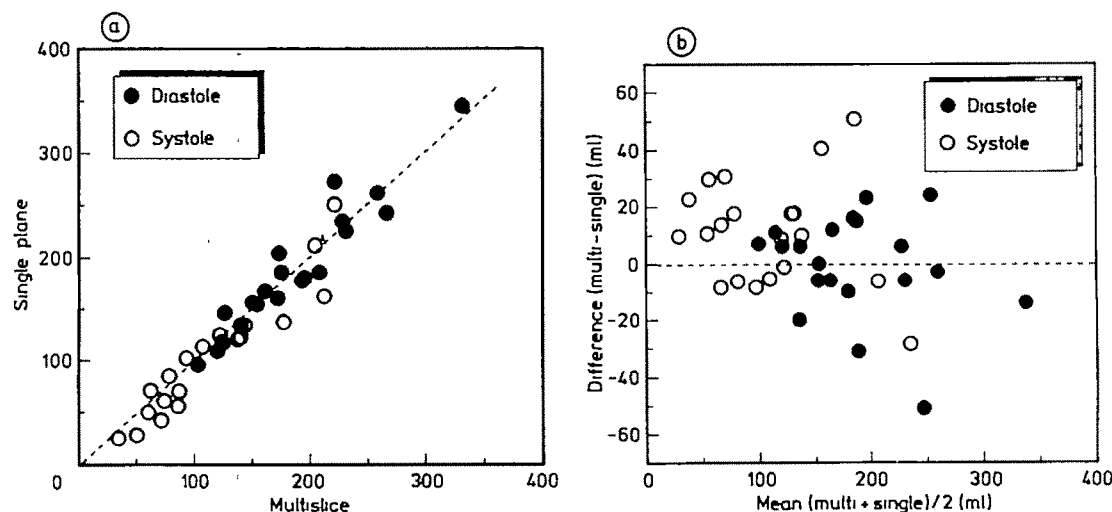


Fig 4 Individual data points for single plane area-length measurements of left ventricular volume and multislice measurements in 20 patients with previous infarction. The dotted line is the line of identity. (b) Difference between measurements plotted against the mean of each pair of measurements.

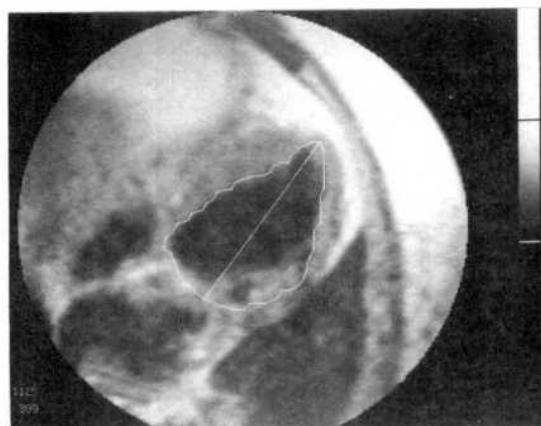


Fig 5 Systolic horizontal long axis image of a patient with previous anterolateral and apical infarction. There is thinning of the lateral wall and apex, and there is intracavitary signal from static blood close to the basal lateral wall. The area of the left ventricular cavity and its long axis are indicated.

117 ml, giving an ejection fraction of 0.35.

Figure 6 compares the ejection fractions calculated from the diastolic and systolic multislice and single plane volumes in the normal subjects and in the patients. In both cases, the mean difference between measurements was significantly less than zero ($p < 0.01$), indicating that the area-length technique overestimated the ejection fraction. The standard deviation of the difference and percentage error were

much smaller in the normal subjects (0.038, 6.2%) than in the patients with infarcts (0.106, 25.7%), indicating that in normal ventricles the area-length technique may lead to errors of up to 0.07 in ejection fraction, but in abnormal ventricles these errors may be as high as 0.21. Inspection of the data shows that much of this error arose in three patients with ejection fractions of approximately 0.20 by the multislice technique, and these were all patients with pronounced wall motion abnormalities.

Figure 7 compares the radionuclide ejection fraction measurements in the patients with those made by magnetic resonance with the multislice technique. Although radionuclide ventriculography underestimated the ejection fraction by a mean of 0.026 ($p < 0.01$), the standard deviation of the difference between measurements was 0.052 which is probably low enough for routine clinical use of the radionuclide technique.

Figure 8 compares the single plane volume measurements in vertical and horizontal long axis planes in the second group of normal subjects. At end systole the mean (SD) difference between measurements (horizontal long axis - vertical long axis) was 6.1 (15.0) ml which was significantly different from zero ($p < 0.05$). At end diastole, the mean (SD) difference (-0.6 (29.3) ml) was not significantly different from zero ($p > 0.05$), although a single spurious point probably affected this result. These differences are sufficiently small for either plane to be suitable for measurement of ventricular volume.

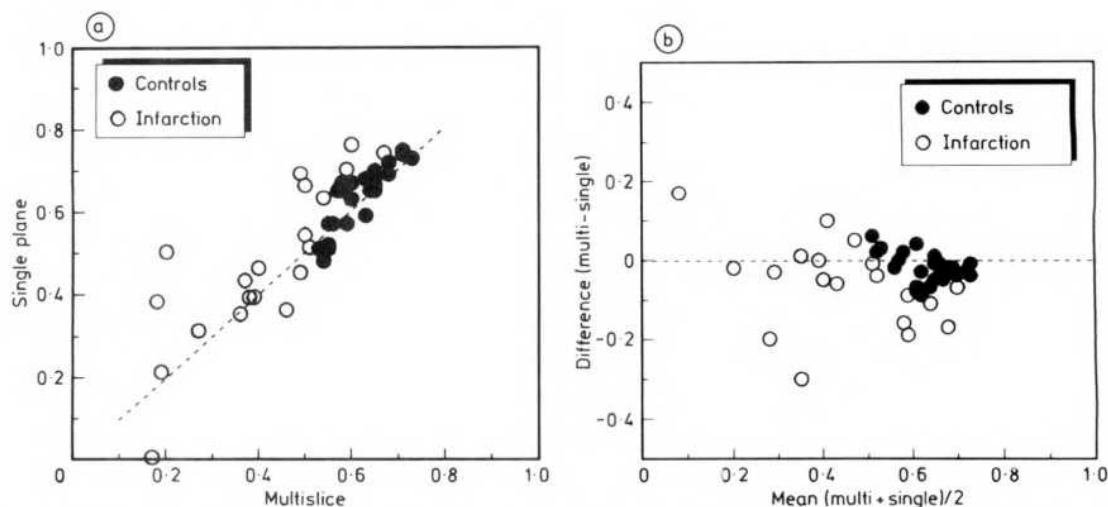


Fig 6 (a) Individual data points for single plane area-length measurements of left ventricular ejection fraction and multislice measurements in 25 normal subjects and 20 patients with previous infarction. The dotted line is the line of identity. (b) Difference between measurements plotted against the mean of each pair of measurements.

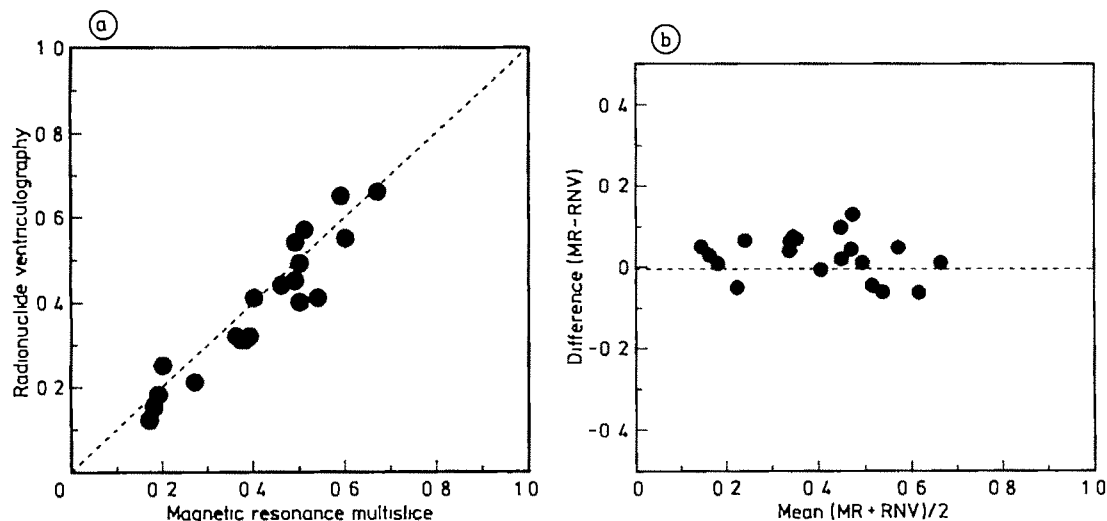


Fig 7 (a) Individual data points for left ventricular ejection fraction measured by radionuclide ventriculography and by the multislice magnetic resonance technique. The dotted line is the line of identity (b) Difference between measurements plotted against the mean of each pair of measurements.

Discussion

The importance of measuring left ventricular volume is highlighted by its long history.⁷ Invasive techniques based on x ray contrast ventriculography have been used for many years, and they assume that the left ventricle is either an ellipsoid or a prolate spheroid. The method first proposed by Chapman *et al*⁸ is similar to the multislice technique used in this

study in that the areas of sections through the left ventricle are summed. The method was too tedious for routine use and it was eclipsed by the methods of Arvidsson⁹ and Dodge *et al*¹⁰ in which the minor axes of the ellipsoid are either measured directly or are calculated from the projected area of the left ventricle. Adaptation of the technique for single plane ventriculograms^{11,12} and for oblique biplane ventriculograms³ has been successful, and the subject has

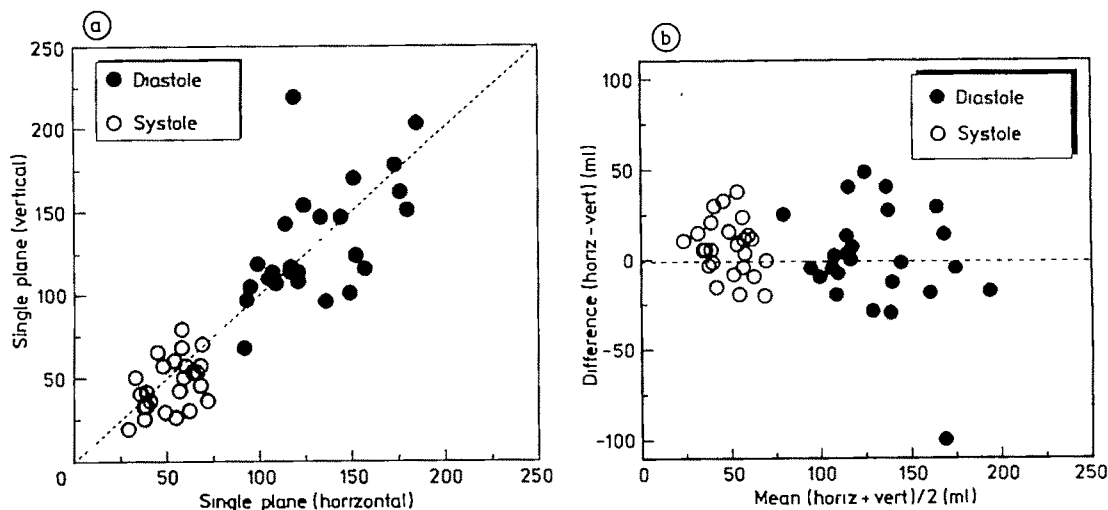


Fig 8 (a) Individual data points for single plane volume measurements in the vertical and horizontal long axis planes in 25 normal subjects. The dotted line is the line of identity. (b) Difference between measurements plotted against the mean of each pair of measurements.

been well reviewed.^{13,14} Both the multislice and the area-length methods used in this study have been extensively studied but their application to magnetic resonance imaging is newer.

Previous studies have investigated magnetic resonance imaging for the determination of left ventricular volume and various techniques have been used. The multislice method is the most accurate because it makes few assumptions about ventricular geometry and it has been validated by a comparison of left and right ventricular stroke volumes in normal subjects.¹⁵ Although there are some sources of error, such as the partial volume effect and ambiguities in defining the endocardium, it is probably the most accurate non-invasive method of measuring left ventricular volume, and it is a suitable standard against which to judge other techniques. It has also been compared with biplane x ray cineangiography¹⁶ and with measurements of cardiac output from indicator dilution¹⁷ and thermodilution,¹⁸ but the invasive nature of these techniques makes them a less suitable comparison. Single plane¹⁹⁻²¹ and biplane²² area-length measurements have also been reported and have been compared with x ray angiography, but there are no reports of a comparison of area-length with multislice measurements.

We have shown that single plane area-length measurements of left ventricular volume agree well with multislice measurements in normal subjects with a mean error throughout the range of volumes of 7.3%, which is adequate for routine clinical use. The mean error is less at end diastole (6.2%) than at end systole (8.8%), suggesting that the ventricle more closely fits the assumed geometry at end diastole. In patients with infarcts the agreement is less good, presumably because of the abnormally shaped ventricle. The mean error throughout the range of volumes is 12.6%, and it is much higher at end systole (16.1%) than at end diastole (9.6%). This is consistent with the assumption that the abnormal ventricle deviates most from an ellipsoid of revolution at end systole. We expected that the correlation would be worst in inferior infarction because the horizontal long axis plane does not include the inferior wall, and errors would be greatest in these patients. No consistent difference was seen between inferior and septal infarction, however, but this may have been because the number of patients was small. In addition, there were few patients in whom the infarct was limited to a single region.

The mean error in ejection fraction measured by the area-length method was also much greater in the abnormal ventricles than in the normal ventricles. The error of 6.2% is adequate for clinical use in normal ventricles, but the error of 25.7% in abnormal ventricles indicates that the single plane

measurements should not be used in patients with previous infarcts.

The comparison of vertical and horizontal long axis volume measurements (fig 8) showed that volumes were slightly higher in the horizontal long axis plane, but the mean difference across the range of volumes was only 2.8 ml. This indicates that in practice both planes are equivalent, but the vertical long axis plane is more familiar to the cardiologist since it is similar to the right anterior oblique ventriculogram. It also requires only a single pilot image to identify the plane and so permits more rapid imaging.

Apart from the assumptions of ventricular geometry, the single plane and biplane techniques for measuring volume make other assumptions that may not always be warranted. The oblique planes were identified at end systole and the same planes were used for the end diastolic images. If the long axis of the ventricle moves between the two, then the end diastolic images may not contain the true long axis. In fact, it is possible to display on an image the line along which any other image cuts it, and hence check that the true long axis is included at end diastole. Separate planes could have been identified for diastole and systole, but this would have lengthened the acquisition time by a further two pilot scans and we did not think that this was necessary for routine measurements.

A further problem in any technique requiring identification of the endocardial surface is the accuracy with which the boundary can be traced. We have previously discussed the problems of edge detection,² but the principal problem in this study was the distinction between myocardium and slowly moving blood within the left ventricular cavity. This problem is apparent in fig 5, but with experience slowly moving blood can usually be distinguished by its high and non-uniform signal. In cases of doubt, a field even echo rephasing sequence can be used.²³ This sequence gives high signal from all non-turbulent blood and low signal from myocardium, and it aids the definition of the endocardial boundary and the distinction of slowly moving blood from thrombus.²⁴

Conclusion

Single plane area-length measurements of left ventricular volume agree well with multislice measurements, which are of proven accuracy, and the agreement is slightly better at end diastole than at end systole in normal ventricles. In patients with previous infarction, the agreement is less good. Ejection fractions calculated from single plane volumes are sufficiently accurate for routine use in

normal ventricles but they should be interpreted with caution in patients with abnormal ventricles. Both the vertical and horizontal long axis planes can be used, but if time is limited the vertical long axis images can be acquired slightly more quickly. In combination with regional wall motion studies from the same images,²³ both global and regional left ventricular function can be assessed in a short time by magnetic resonance imaging.

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Pulmonary embolectomy for acute massive pulmonary embolism: an analysis of 71 cases

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SUMMARY Between 1964 and 1986 a total of 71 pulmonary embolectomies were performed for acute massive pulmonary embolism. All patients were severely compromised haemodynamically. Sixteen (64%) of 25 patients who had sustained significant periods of cardiac arrest before operation died. The principal cause of death in this group was severe neurological damage. Five (11%) of the 46 who had not had a cardiac arrest died. The 50 (70%) patients who survived did so largely without morbidity during their hospital admission and in the follow up period. Most were not treated with long term anticoagulants and only two had another embolism.

When a patient with acute massive pulmonary embolism is too ill to be given thrombolytic treatment, or when thrombolysis is either contraindicated or too slow in producing benefit, pulmonary embolectomy remains an effective alternative treatment with an acceptable mortality.

Acute massive pulmonary embolism is a life threatening disorder that must be treated immediately. Some believe that there are no indications for embolectomy¹ while others justify prophylactic open embolectomy.² This debate was particularly intense in the early 1970s once thrombolytic treatment was shown to hasten the resolution of pulmonary emboli.^{3,4} Although we often use thrombolytic agents to manage patients with acute massive pulmonary embolism we continue to refer patients for pulmonary embolectomy. We report the indications for this operation and our experience of its use in 71 patients.

Patients and results

Between 1964 and 1986 a total of 139 patients were admitted to the Brompton Hospital with acute massive pulmonary embolism. Until 1968 heparin was the only available drug and therefore all 30 patients with acute massive pulmonary embolism admitted during this period had pulmonary embolectomy. After 1968 streptokinase became available and was

given to 68 patients, some of whom are described elsewhere.⁵ Although the introduction of thrombolytic treatment reduced the annual number of pulmonary embolectomies this operation was performed in 41 of 109 patients with acute massive pulmonary embolism. Sixteen patients (39%) had a definite contraindication to thrombolytic treatment (major surgery within the last week ($n = 10$), pregnancy ($n = 2$), haemorrhagic eye disease ($n = 1$), active gastrointestinal bleeding ($n = 1$), active ulcerative colitis ($n = 1$), and lung cavitation ($n = 1$) and 13 (32%) were considered to be too ill for a trial of streptokinase. Two patients (5%) started on streptokinase but they deteriorated and were referred for operation. A further five (12%) patients had undergone a major operation 8-14 days before their acute massive pulmonary embolism, and in the early days of our experience with thrombolysis we regarded this as a relative contraindication. In four patients (10%) thrombolytic treatment could have been given but pulmonary embolectomy was regarded as the best treatment.

So over 23 years 71 pulmonary embolectomies were performed (49 women, mean age 39.4 years, range 17-68 and 22 men, mean age 51.2 years, range 15-75). All patients had a clinical diagnosis of massive pulmonary embolism and an appreciable impairment of haemodynamic function. Twenty five patients (35%) had required clinically significant periods of external massage before operation because

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of severe circulatory collapse. The patients' symptoms had started less than 24 hours before in 65% and between 24 and 48 hours before in 25%. Seven patients (10%) had had documented symptoms suggestive of pulmonary emboli for 3-7 days but were referred only when a further acute episode resulted in major deterioration in haemodynamic function.

Potential risk factors for the development of pulmonary emboli included recent operation in 41 patients (58%), the contraceptive pill in nine (13%), and pregnancy in five (7%). Twenty three patients (32%) were considered to be too ill to undergo pulmonary angiography and in a further 13 (18%) patients cardiac catheterisation was believed to be unnecessary because the diagnosis of acute massive pulmonary embolism was clinically certain. These 36 patients were referred immediately for operation and in all cases the diagnosis was confirmed then. Thirty five (50%) underwent right heart catheterisation. Mean pressures (mm Hg) for the group were as follows: right atrium (mean) = 11, right ventricular systolic = 45, mean pulmonary artery = 29. Mean arterial oxygen saturation was 40% in the pulmonary artery and 86% in a systemic artery. Pulmonary arteriography was performed in all catheterised patients; this showed pulmonary emboli that occupied > 50% of the pulmonary arterial tree. There was often a transient worsening of hypotension after the injection of contrast but this resolved rapidly. Three patients (9%) required short periods of external cardiac massage (< 1 minute) after angiography but were quickly resuscitated and are not included in the group of 25 patients described above who required "considerable" periods of external cardiac massage.

Sixty four (90%) of the 71 pulmonary embolectomies were undertaken by one surgeon (MP) and all were performed on full cardiopulmonary bypass. The mean perfusion time was 27 minutes. Four patients were put on partial (femoro-femoral) bypass before the start of full bypass.

DEATHS (TABLE 1)

Twenty one patients (29.6%) died during their hospital admission and 16 of these had required considerable periods of external cardiac massage before operation. Three of these 16 died on bypass, nine died within four weeks with severe neurological damage, three died in the first postoperative week of circulatory or multisystem failure, and one died at five weeks of carcinomatosis. Of the five patients who died without having had preoperative external cardiac massage one died on bypass, one died of pleural bleeding, and one of gastrointestinal bleeding; one patient died within 24 hours of persistent hypotension; and one died at six days after ilio caval thrombectomy for extensive venous occlusion. The

Table 1 Causes of death in patients undergoing pulmonary embolectomy who had had external cardiac massage (+ ECM) before operation and those who had not (- ECM)

Deaths (21/71, 29.6%)	+ ECM (%)	- ECM (%)
On cardiopulmonary bypass	3 (14)	1 (5)
Neurological	9 (43)	
Circulatory/multisystem failure	3 (14)	1 (5)
Carcinomatosis	1 (5)	
Haemorrhage		2 (10)
Massive venous occlusion		1 (5)
Total	16 (76)	5 (24)

mortality was 64% in patients who had required preoperative external cardiac massage and 11% in those who had not.

SURVIVORS (TABLE 2)

Fifty (70.4%) patients survived to leave hospital; nine of them had required preoperative external cardiac massage. One of the 50 survivors needed haemodialysis but then made a full recovery, three had moderate neurological deficits that were thought to have been present before operation, and in one hemiplegia developed after operation. This was thought to have been caused by a paradoxical embolus through a patent foramen ovale.

After discharge from hospital seven (14%) patients were lost to follow up but data were available from general practitioner and hospital records on the remaining 43 (86%). Four (8%) patients died during follow up, one of carcinoma at 20 months, one of peritonitis at 12.5 years, one after a mitral valve replacement at 15 years, and one patient with nephrotic syndrome died of peritonitis five months after embolectomy. During his terminal illness the last patient had a further pulmonary embolus. We do not know whether he was taking anticoagulants at the time.

The 39 patients who were still alive at the last recorded attendance have been followed up for a total of 335 patient years (mean duration of follow up 9.4 months, range 1-254). All have remained well and in only one patient was there any suggestion of a further

Table 2 Morbidity in patients who survived pulmonary embolectomy and who had had external cardiac massage before operation (+ ECM) and those who had not (- ECM)

Survivors (50/71, 70.4%)	+ ECM (%)	- ECM (%)
Full recovery	8 (16)	37 (74)
Temporary haemodialysis		1 (2)
Moderate neurological damage:		
Present before operation	1 (2)	2 (4)
Developed after operation		1 (2)
Total	9 (18)	41 (82)

pulmonary embolus. In this patient, who also had nephrotic syndrome, some pleuritic chest pain developed but no other clinical features of pulmonary embolism and he was advised to restart warfarin. Subsequently he remained well.

ANTICOAGULATION

We usually advise patients to remain on anticoagulants for 3–6 months after operation. When we reviewed the clinical information we could not be certain how long 12 (28%) of the 43 patients for whom follow up data were available were treated with anticoagulants. Twenty two (71%) of the remaining 31 patients took warfarin for less than six months and a further two (6%) took it for up to one year. One patient required long term anticoagulation for mitral valve disease and six (19%) continued warfarin out of personal preference or on the advice of their medical practitioner. Thus 24 (77%) of the patients for whom information was available were not on long term anticoagulants. It seems likely that the proportion was similar in those for whom anticoagulant data were not available. Thus most survivors had only short courses of oral anticoagulants and, of these, one had a definite further pulmonary embolus as part of terminal illness and one otherwise fit individual may have had an acute minor embolism. At worst this represents a recurrence rate of 4.6%.

Discussion

The lung has an active fibrinolytic system and most pulmonary emboli resolve spontaneously^{6,7} over a few weeks.^{8–10} This spontaneous resolution makes it likely that many smaller emboli go undetected clinically.¹¹ Clinically apparent episodes result in various syndromes, from "acute minor" to "acute massive" pulmonary embolism.¹² Patients with little or no circulatory impairment after a pulmonary embolus can be treated symptomatically with anticoagulants such as heparin¹³ to reduce the likelihood of further emboli. Patients in this group are clearly not candidates for pulmonary embolectomy. Acute massive pulmonary embolism results in appreciable haemodynamic disturbance^{14,15} and carries a high mortality.^{16–18} Vigorous treatment for this group is mandatory but the choice of the most appropriate treatment has been the subject of some debate. There are two main alternatives—thrombolytic treatment and pulmonary embolectomy. Thrombolytic agents such as streptokinase,^{3,4} urokinase,^{19,20} and recombinant tissue plasminogen activator (rt-PA)^{21,22} were effective in lysing pulmonary emboli and acted more quickly than heparin.^{3,4} Controlled and uncontrolled trials showed that mortality tended to be lower in patients treated

with thrombolysis than with heparin.^{20,23,24} These differences did not reach statistical significance. None the less, a more rapid resolution of pulmonary emboli seems desirable because prolonged haemodynamic disturbance can only cause harm, and if further emboli develop their haemodynamic effect will be lessened if previous emboli have been partially removed. Thus the case for the urgent use of thrombolytic agents in patients with acute massive pulmonary embolism is powerful and our experience supports this view.^{3,5,24}

Opinions on the place of pulmonary embolectomy vary considerably. Some claim that there are no indications for the operation¹ while others believe that prophylactic open pulmonary embolectomy can be justified.² It has been argued that pulmonary embolectomy is seldom a practical procedure²⁵ because few patients survive long enough for the procedure to be undertaken and that those who do are likely to survive anyway.¹ There is some truth in this, because although pulmonary embolectomy can be performed without cardiopulmonary bypass with acceptable results,²⁶ most patients who require operation for acute massive pulmonary embolism in the United Kingdom are transferred to a regional cardiothoracic centre. Inevitably some patients will die before or during transfer but a significant number with acute massive pulmonary embolism will deteriorate some hours after the initial embolic episode²⁷ suggesting that although the risk of death declines with time it is not abolished. This has certainly been our experience; most patients in our series were transferred from other hospitals and were still severely compromised haemodynamically.

Although it has proved difficult to define these patients who are considered too ill to undergo a trial of thrombolytic treatment this does not deny their existence and 32% of the patients in this series belonged to this group. Clearly decisions regarding operation have to be made for individual patients but we think that some patients are so severely compromised haemodynamically by their massive pulmonary embolus that subjecting them to a trial of thrombolytic treatment is inappropriate and they should have pulmonary embolectomy. Also, even though the contraindications to thrombolytic treatment have relaxed with increasing experience in the use of these drugs, there is still a significant number of patients for whom thrombolytic treatment is believed to be inadvisable—they include patients who have recently undergone major operations or had a cerebrovascular accident, and those with active peptic ulceration or bleeding diatheses. These patients, together with the few who deteriorate haemodynamically after starting thrombolytic treatment seem to be suitable candidates for

embolectomy. Unfortunately there has been no randomised trial of embolectomy and thrombolytic or anticoagulant treatment and there is unlikely to be one of sufficient size to be of value. This is because it is unethical to withhold embolectomy if a patient randomised to thrombolytic treatment deteriorates; this makes treatment failure a necessary end point as well as death. Also, few suitable patients with acute massive pulmonary embolism and significant haemodynamic impairment are likely to be recruited in any one centre. We therefore have had to turn to the published reports of clinical experience of this operation and make informed forecasts about likely benefit.

Many cases of pulmonary embolectomy have been reported since Trendelenburg's description in 1908.^{28,29} Recently these were reviewed by Del Campo who calculated an overall mortality of 40% for embolectomies performed on cardiopulmonary bypass.²⁷ However, these results include early experiences where the reported mortality was often high. The subsequent reduction in mortality was at least partly related to the recognition that anaesthetic agents had profound hypotensive effects that were often fatal^{27,30} and could be prevented by vasopressor agents.

Twenty one (29%) of our series of 71 patients died in hospital. But mortality was considerably lower (5/46, 11%) in patients who had not sustained a cardiac arrest before operation than in those who had (16/25, 64%). We do not know how our patients would have fared if they had not had embolectomy. But we believe that it was of benefit.

Morbidity in patients undergoing pulmonary embolectomy was principally neurological. In most this damage was believed to have occurred before operation, usually as a result of a cardiac arrest. The outcome was good in patients who reached the operating theatre without needing external cardiac massage. Although most patients were not given long term anticoagulants the frequency of recurrent pulmonary emboli in the follow up period was low (4.6%). This accords with the view that long term anticoagulants are unnecessary³¹ and that for patients who have an isolated episode of massive pulmonary embolism procedures to place or place filters in the inferior vena cava are inappropriate. These procedures should probably be reserved for the few patients who have recurrent pulmonary emboli and in whom oral anticoagulation is either contraindicated or fails to prevent recurrence.^{32,33}

We use thrombolysis to treat acute massive pulmonary embolism unless such drugs are contraindicated or haemodynamic function is severely compromised. We believe pulmonary embolectomy provides an effective alternative treatment with an

acceptable mortality in these two groups and in those who deteriorate on thrombolytic treatment.

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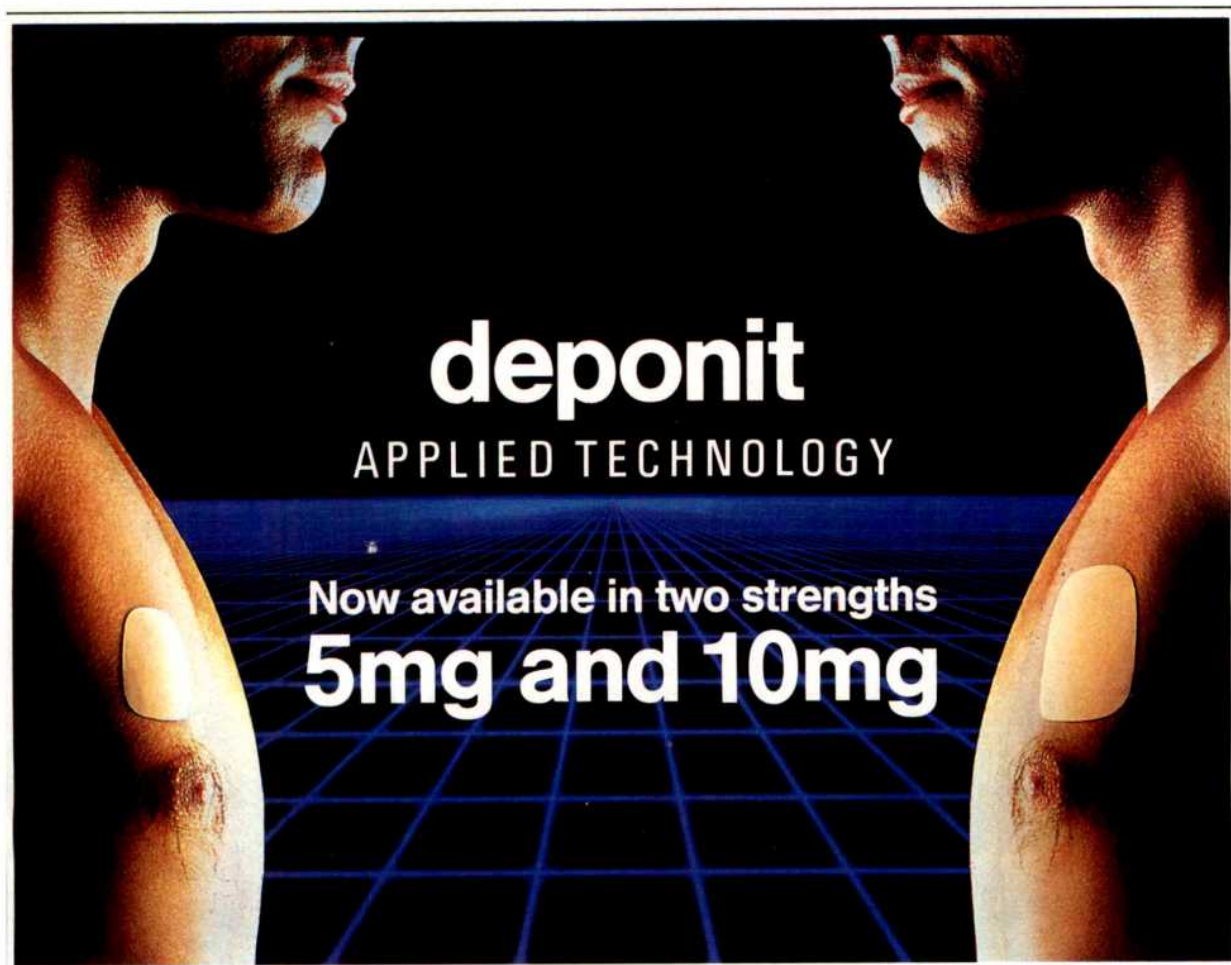
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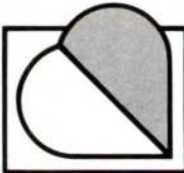
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Thrombin and plasmin activity in coronary artery disease

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SUMMARY Basal plasmin and thrombin activity in plasma were assessed by radioimmunoassay of the fibrinogen derivatives containing the sequence B β ₁₅₋₄₂ and of fibrinopeptide A respectively in a cross sectional controlled study of men with coronary artery disease. Compared with healthy controls (n = 33) men with angiographically defined coronary artery disease (n = 98) had a modest but significant increase in concentrations of fibrinopeptide A, indicating an activated coagulation system. Concentrations of B β ₁₅₋₄₂ were similar in those with coronary artery disease and in the controls.

The enhanced thrombin activity in coronary artery disease is in keeping with current evidence suggesting an association between coronary artery disease and a hypercoagulable state.

Recent interest in the role of haemostasis in vascular disease was prompted by studies showing an association between haemostatic variables and ischaemic heart disease¹⁻³ and by prospective studies which show that increased fibrinogen, in particular, is associated with ischaemic heart disease.⁴⁻⁶ Sensitive radioimmunoassays have become available for measurement of the fibrinogen derivatives, fibrinopeptide A (an indicator of thrombin degradation of fibrinogen in vivo) and B β ₁₅₋₄₂-containing peptides (an indicator of plasmin mediated fibrin(ogen)-olysis). Simultaneous measurement of these peptides permits the balance between fibrinolysis and coagulation to be estimated. Since it has been postulated that the patency of the vascular system depends on the dynamic equilibrium between fibrinolysis and coagulation,⁷ these peptides could provide a measure of the risk of thrombosis.⁸ Compared with control subjects, fibrinopeptide A concentrations have been reported to be raised⁹ or normal¹⁰ in subjects with ischaemic heart disease. The concentrations of B β ₁₅₋₄₂ peptides in patients with coronary artery disease have not been studied and therefore we have measured these fibrinogen derivatives in a controlled study to establish whether coronary artery disease is associated with an imbalance between fibrinolysis and coagulation.

Patients and methods

Informed consent was obtained from 98 white men who had been admitted for elective coronary angiography for investigation of ischaemic cardiac pain. Because acute arterial vascular events have been shown to alter some tests of haemostasis^{11,12} we excluded patients who had sustained a myocardial infarction within three months of coronary investigation. We studied a control group of 33 white, healthy factory employees. These men lived in the same area as the patients with coronary disease. The control subjects were not receiving any drug treatment, were not hypertensive (blood pressure < 160/95 mm Hg), and gave no family history of ischaemic heart disease or diabetes mellitus. Random urinalysis and the measurement of concentrations of plasma glucose in fasting subjects excluded undiagnosed asymptomatic diabetes mellitus. The body mass index (weight (kg)/height (m²)) was calculated as a measure of overweight or underweight.¹³

METHODS

A single resting blood sample was taken with minimal venostasis from fasted subjects between 7 and 9 am. Citrated blood was taken for radioimmunoassay of plasma B β ₁₅₋₄₂ peptides and fibrinopeptide A (IMCO, Stockholm) as previously described.^{14,15} Coronary angiography was performed by the Judkins' technique¹⁶ and blood samples were taken before this procedure. Coronary artery disease was

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scored as the number of major vessels with a reduction of the luminal diameter of $\geq 50\%$.

STATISTICAL ANALYSIS

The distribution of fibrinopeptide A and $B\beta_{15-42}$ peptides was skewed. Log transformation provided the best approximation to a normal distribution. The principal aim of the study was to assess whether the peptide concentrations were different in coronary heart disease and this was analysed by the unpaired Students *t* test on log transformed data. A one factor analysis of variance (ANOVA) was used to assess the effect of the severity of coronary artery disease on the peptide concentrations.

Results

The two groups were well matched for age, body mass index, and smoking (table). The table lists the log transformed values for $B\beta_{15-42}$ and fibrinopeptide A. Concentrations of $B\beta_{15-42}$ were similar in the controls and in the patients with coronary artery disease. Fibrinopeptide A concentrations were higher in patients with coronary artery disease ($p < 0.05$) than in controls. When the log data on the four groups (controls and patients with one, two, or three vessel disease) were evaluated by one factor ANOVA, the differences were not statistically significant (*F* value 2.249, $p = 0.08$), although in patients with two and three vessel disease mean fibrinopeptide A concentrations were 48% and 39% higher than in the controls (figure). Peptide concentrations in patients with a previous myocardial infarction ($n = 55$) were similar to those in patients with coronary artery disease but no previous thrombotic event ($n = 43$), and antianginal treatment (β adrenoceptor blockade, calcium channel antagonists, nitrates) did not influence either $B\beta_{15-42}$ or fibrinopeptide A concentrations.

Table Clinical and haemostatic variables (mean (SD)) in men with coronary artery disease (CAD) and controls

	Controls	CAD
Number	33	98
Age (years)	46.5 (6.1)	49.6 (8.3)
Body mass index	25.7 (2.4)	26.1 (2.3)
Smokers (%)	11 (33)	42 (43)
Fibrinopeptide A (pmol/ml)	1.61 (1.31-1.96)	2.09* (1.84-2.37)
$B\beta_{15-42}$ (pmol/ml)	2.06 (1.12-3.34)	1.63 (1.36-1.94)

Fibrinopeptide A and $B\beta_{15-42}$ are given as mean and 95% confidence intervals

* $p < 0.05$ compared with controls.

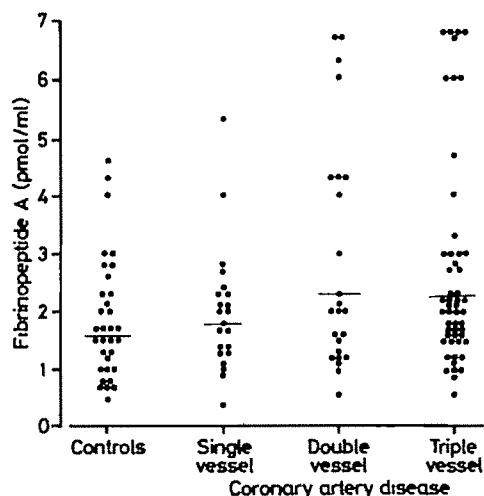


Figure Concentrations of fibrinopeptide A in controls and in patients with coronary artery disease subdivided according to the extent of coronary artery disease. The horizontal bar indicates the geometric mean value.

Discussion

We found a modest but significant increase in fibrinopeptide A in patients with coronary artery disease, indicating an increase in thrombin degradation of fibrinogen in such patients. This result accords with a previous study.⁹ Although there were no statistically significant differences in fibrinopeptide A concentrations between patients with coronary artery disease of varying severity, the higher concentrations in patients with double and triple vessel disease may be biologically important.

Earlier studies did not examine $B\beta_{15-42}$ concentrations in coronary artery disease and we did not find any differences in unstimulated, resting $B\beta_{15-42}$ concentrations between patients and healthy controls. This finding could be interpreted in two different ways. The obvious suggestion is that plasmin-mediated fibrin(ogen)olysis is not altered by the presence of coronary artery disease. Alternatively, an activated coagulation system (as shown by raised fibrinopeptide A concentrations) could lead to a secondary activation of fibrinolysis, and the absence of an increase in $B\beta_{15-42}$ concentrations may reflect an abnormal response of the fibrinolytic enzyme system. Dynamic tests of plasma fibrinolytic potential showed that abnormalities of fibrinolysis are more common in men with ischaemic heart disease^{3,17,18} and more recent studies have shown that this finding may be related to high concentrations of the fast-acting inhibitor to tissue plasminogen activator.¹⁹⁻²¹ It may

be that dynamic stimuli such as exercise or venous occlusion might unmask defective plasmin activity (as measured by changes in $B\beta_{1-42}$ concentrations) in coronary artery disease but this suggestion requires further study. None the less, the results of our study accord with growing evidence that ischaemic heart disease is associated with haemostatic disturbance.¹⁻³

We thank Dr G Gettinby for statistical advice.

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Left ventricular function at rest and during exercise in acute hypothyroidism

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SUMMARY The effect of hypothyroidism on left ventricular function at rest and during exercise was studied in nine patients without demonstrable cardiovascular disease who had had total thyroidectomy and ablative radioiodine treatment for thyroid cancer. Radionuclide ventriculography and simultaneous right heart catheterisation were performed while the patients were hypothyroid two weeks after stopping triiodothyronine treatment (to permit routine screening for metastases) and while they were euthyroid on thyroxine replacement treatment. When the patients were hypothyroid, cardiac output, stroke volume, and end diastolic volume at rest were all lower and peripheral resistance was higher than when they were euthyroid. Pulmonary capillary wedge pressure, right atrial pressure, heart rate, left ventricular ejection fraction, and the systolic pressure:volume relation of the left ventricle, which was used as an estimate of the contractile state, were not significantly different when the patients were hypothyroid or euthyroid. During exercise, heart rate, cardiac output, end diastolic volume, and stroke volume were higher when the patients were euthyroid than when they were hypothyroid. Again, pulmonary capillary wedge pressure, ejection fraction, and the systolic pressure:volume relation were similar in both thyroid states.

The data suggest that the alterations in cardiac performance seen in short term hypothyroidism are primarily related to changes in loading conditions and exercise heart rate; they do not suggest that acute thyroid hormone deficiency has a major effect on the contractile properties of the myocardium.

Thyroid hormone deficiency is known to affect the heart.¹⁻³ Although exercise intolerance is a classic feature of hypothyroidism, most studies have focused on the contractile function of the heart at rest⁴⁻⁶ and little attention has been paid to the performance of the left ventricle during exercise.

Some radionuclide studies assessed the response of the ejection fraction to stress in hypothyroid patients.⁷⁻⁹ The ejection fraction is widely accepted as a useful measure of ventricular performance¹⁰ but it has limitations. Because it is the ratio of two physiological variables the size of the left ventricular chamber can change considerably without causing a significant change in ejection fraction. So the

haemodynamic consequences of hypothyroidism are only incompletely evaluated by the response of the ejection fraction to stress, and for a more comprehensive assessment left ventricular volumes and pressures must be measured. More importantly, the ejection fraction is dependent not only on the intrinsic contractile state of the heart but also on the preload and afterload.¹¹ Changes in loading conditions seem to be especially important when thyroid function is abnormal¹² and, therefore, it is unreliable to infer the level of contractile activity from the change in ejection fraction when the euthyroid state is restored.

We used radionuclide angiography and right heart catheterisation to assess the response of the left ventricle at rest and during exercise to severe short term hypothyroidism. We attempted to distinguish between the effects on the heart's loading conditions and the effects on contractility.

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Patients and methods

STUDY GROUP

We studied five women and four men aged 18 to 56 years (mean (SD) 43 (13) years). The patients had undergone total thyroidectomy and ablative radioiodine treatment for thyroid cancer 22 to 89 months (63 (23) months) before the current study and they were free of metastases at regular follow up examinations. None of the patients was hypertensive or had evidence of cardiovascular disease on the basis of history, clinical examination, chest radiographs, resting electrocardiogram, and exercise electrocardiogram. When they were hypothyroid none of the patients had a pericardial effusion shown by echocardiography. Except for thyroxine, no patient was taking any drugs at the time of cardiac assessment. The purpose of the study was fully explained to each patient and their informed written consent was obtained.

All patients were studied at rest and during supine bicycle exercise when they were euthyroid by clinical and laboratory standards and when they were hypothyroid after replacement treatment with thyroid hormones had been stopped to permit a routine iodine-131 total body scan for metastases.

In four patients the initial study was performed while they were taking thyroxine and were euthyroid. Then thyroxine was replaced by triiodothyronine five weeks before the second study, which was carried out two weeks after triiodothyronine was stopped. The remaining five patients were first studied when they were hypothyroid after long term replacement treatment with thyroxine had been stopped. After the study was completed, treatment with thyroxine was re-started at an initial daily dose of 0.9 nmol/kg body weight. The dosage was increased by increments of 0.9 nmol/kg body weight every five weeks until the thyrotropin releasing hormone test was normal. The patients were restudied when they had been clinically and biochemically euthyroid for at least six weeks.

ASSAYS

Serum concentrations of thyroxine, triiodothyronine, and thyrotropin were measured by commercial radioimmunoassays (T4 and T3 RIA kits from Bayer AG, Leverkusen, West Germany, and TSH IRMA from Behringwerke AG, Marburg, West Germany). The sensitivity was 6.4 nmol/l for thyroxine, 0.3 nmol/l for triiodothyronine, and 0.02 mU/l for thyrotropin. The uptakes of thyroxine and triiodothyronine were measured to detect any alterations in hormone binding and the free thyroxine equivalent and the free triiodothyronine equivalent were calculated. All samples were analysed in duplicate in a single radioimmunoassay run. In this

laboratory, the normal ranges for serum concentrations of thyroxine and triiodothyronine are 51.5–154.4 nmol/l and 1.23–2.76 nmol/l respectively. The upper limit of normal for basal thyrotropin is 4 mU/l and the normal range of thyrotropin 20 minutes after intravenous administration of 200 µg of thyrotropin releasing hormone is 2–30 mU/l.

RADIONUCLIDE AND CATHETERISATION TECHNIQUES

The baseline heart rate was recorded one hour before the study and the change in heart rate after cardiac instrumentation was regarded as an index of the individual anxiety level prompted by cardiac catheterisation. In the nuclear imaging laboratory a Swan Ganz 7F thermodilution catheter was passed to the pulmonary artery via an antecubital vein under continuous pressure monitoring. Right atrial and pulmonary artery pressures were measured with a P-23 Statham strain gauge from a reference level 5 cm below the sternal angle. Blood pressure was measured by a standard cuff sphygmomanometer. The electrocardiogram was recorded throughout the study. Cardiac output was measured in triplicate by the thermodilution technique. Saline injections were started at end exhalation.¹³

The patients were injected with 20 mCi (740 MBq) of technetium-99m for in vivo labelling of red blood cells and were imaged in the modified left anterior oblique position. The left ventricular ejection fraction was measured from the background-corrected time activity curve with a fully automated edge detection algorithm. Regional wall motion was assessed by the Fourier analysis of radionuclide ventriculograms. These radionuclide techniques have been described earlier.¹⁴

The patients were already familiar with supine exercise from a previous practice session.¹⁵ After acquisition of haemodynamic and radionuclide data at rest, single level supine exercise was carried out at a workload of 100 W in six patients. In two patients who were limited by severe muscle weakness when hypothyroid, the workload was reduced to 75 W in both studies and one subject was exercised at 50 W. Imaging started four minutes after the start of the stress test to ensure a steady state. The haemodynamic measurements were made during the sixth minute of exercise.

DERIVED HAEMODYNAMIC VARIABLES

Derived haemodynamic variables were calculated as follows:

Left ventricular end diastolic volume (ml) = stroke volume:ejection fraction

Systemic vascular resistance [dyn.s.cm^{-5}] = $80 \times$ (mean arterial pressure—mean right atrial pressure) $\div$ cardiac output.

The mean arterial pressure was calculated as the diastolic pressure plus one third of the pulse pressure. Systemic vascular resistance was not calculated for the exercise studies because we find that sphygmomanometric measurements of the exercise diastolic blood pressure are unreliable.

Left ventricular end systolic volume (ml) = end diastolic volume — stroke volume.

Left ventricular systolic pressure:volume ratio [mm Hg/ml] = sphygmomanometric systolic blood pressure — left ventricular end systolic volume.

STATISTICAL ANALYSIS

Wilcoxon's test for paired observations was used for statistical analysis. All results are given as the mean (1 SD) unless stated otherwise. A probability value of $p < 0.05$ was regarded as statistically significant.

Results

THYROID STUDIES

Table 1 shows the biochemical data. The daily dose of thyroxine required for a normal thyrotropin releasing hormone test ranged from 97 nmol to 322 nmol (mean 214 (71)).

HAEMODYNAMIC DATA

When the patients were euthyroid the haemodynamic and radionuclide measurements were consistently within normal limits. Standardisation of cardiac output and left ventricular volumes for body surface did not change the significance values of any data. Whether the patients were first studied when they were euthyroid or when they were hypothyroid had no discernible effect on the test outcomes. The heart rate an hour before the study was similar to that recorded upon completion of cardiac instrumentation in both euthyroid and hypothyroid patients, suggesting that the anxiety level associated with right heart catheterisation was low (68 (12) v 70 (11) beats/min and 81 (15) v 80 (14) beats/min respectively).

Table 1 Concentrations of serum thyroid hormones in nine athyreotic patients when hypothyroid and when euthyroid on thyroxine replacement

	Hypothyroid	Euthyroid	Normal range
Total T4 (nmol/l)	8.2 (2.5)	128.7 (24.5)	51.5–154.4
FT ₄ E	0 (0)	0.81 (0.29)	0.28–1.21
Total T3 (nmol/l)	0.52 (0.37)	2.21 (0.63)	1.23–2.76
FT ₃ E	0.06 (0.04)	0.59 (0.28)	0.4–0.8

Values are mean (1 SD).

T₄, thyroxine; FT₄E, free thyroxine equivalent; T₃, triiodothyronine; FT₃E, free triiodothyronine equivalent.

Table 2 Haemodynamic and radionuclide data at rest in nine athyreotic patients without demonstrable cardiovascular disease when hypothyroid and when euthyroid on thyroxine replacement

Variable	Hypothyroid	Euthyroid
Heart rate (beats/min)	70 (11)	80 (14)
Systolic blood pressure (mm Hg)	124 (14)	134 (22)
Pulmonary capillary wedge pressure (mm Hg)	6 (2)	8 (2)
Right atrial pressure (mm Hg)	3 (2)	4 (2)
Cardiac output (l/min)	4.0 (0.6)	5.8 (1.0)†
Stroke volume (ml)	58 (9)	74 (13)†
End diastolic volume (ml)	90 (19)	106 (18)*
End systolic volume (ml)	32 (11)	32 (7)
Ejection fraction (%)	66 (6)	70 (4)
Left ventricular systolic pressure:volume relation (mm Hg/ml)	4.4 (1.8)	4.2 (0.7)
Total peripheral resistance (dyn.s.cm^{-5})	2105 (490)	1438 (297)†

Values are mean (1 SD). Differences were analysed by the Wilcoxon test for paired observations (* $p < 0.05$; † $p < 0.01$).

Table 2 summarises the haemodynamic and radionuclide data at rest. Resting hypothyroid and euthyroid values were similar for right atrial pressure

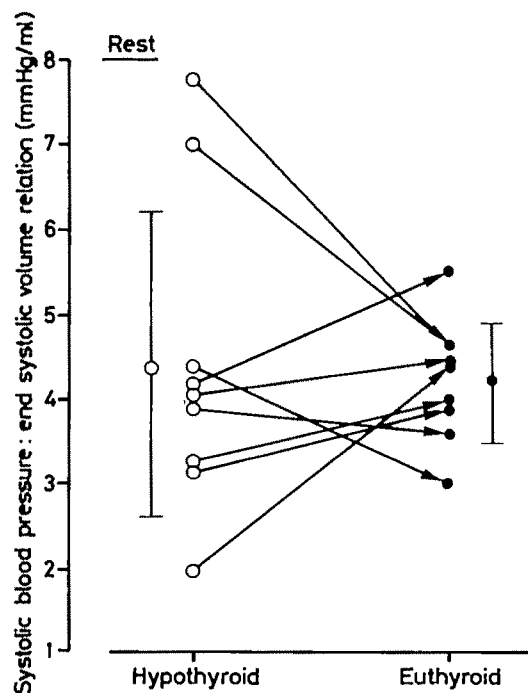


Fig 1 Individual and group mean values for the left ventricular systolic pressure:volume ratio in the hypothyroid (left) and in the euthyroid state (right) at rest. Overall, concentrations of thyroid hormones had no significant effect on this variable, which is used as an estimate of the contractile state of the left ventricle.

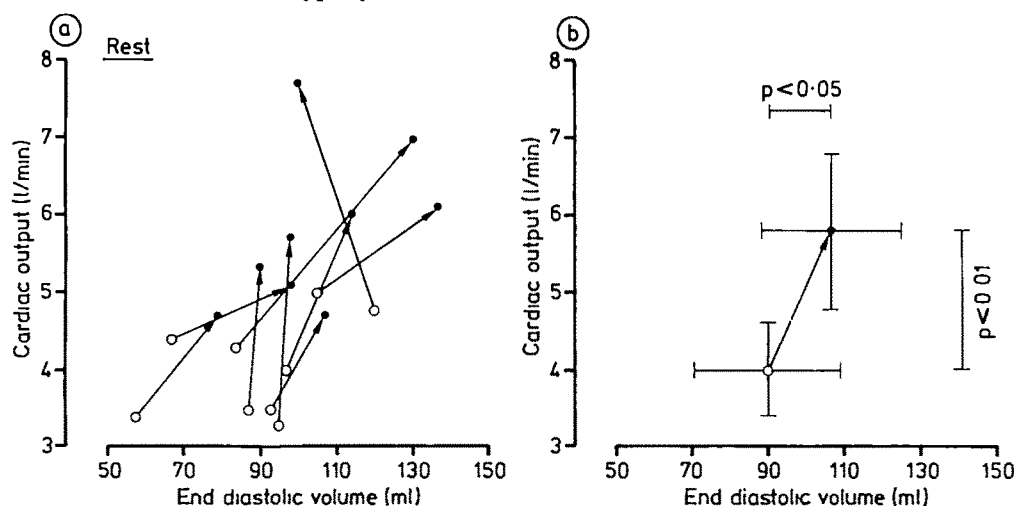


Fig 2 Relation between left ventricular end diastolic volume and cardiac output at rest in the hypothyroid (○) and in the euthyroid (●) state. (a) The arrows joining two points represent changes in the value for individual patients. (b) The group mean (1 SD) values. A change from the hypothyroid to the euthyroid state was accompanied by a significant increase in both cardiac output ($\Delta = 45$ (19)%, $p < 0.01$) and left ventricular end diastolic volume ($\Delta = 21$ (22)%, $p < 0.05$).

(3 (2) v 4 (2) mm Hg), pulmonary capillary wedge pressure (6 (2) v 8 (2) mm Hg), and mean arterial pressure (105 (10) v 106 (15) mm Hg). Similarly, hypothyroidism had no significant effect on end systolic volume (32 (11) v 32 (7) ml), on left ventricular ejection fraction (66 (6) v 70 (4) %), and on the systolic pressure:volume ratio of the left ventricle (4.4 (1.8) v 4.2 (0.7) mm Hg/ml) (fig 1). The values for heart rate tended to be higher in euthyroid patients (70 (11) v 80 (14) beats/min) but this difference did not reach statistical significance. The ejection fraction was above 55% in all patients. Cardiac output (4.0 (0.6) v 5.8 (1.0) l/min ($p < 0.01$) $\Delta = 45$ (19)%), stroke volume (58 (9) ml v 74 (13) ml

($p < 0.01$) $\Delta = 27$ (13)%), and end diastolic volume (90 (19) ml v 106 (18) ml ($p < 0.05$) $\Delta = 21$ (22)%) were all lower when the patients were hypothyroid. Figure 2 shows the individual changes in cardiac output and the corresponding changes in end diastolic volume; individual haemodynamic responses to thyroid hormone deficiency were uniform. When a patient was hypothyroid, cardiac output was always lower and end diastolic volume was smaller in all but one case. Total peripheral resistance decreased substantially when the patients became euthyroid (2105 (490) v 1438 (297) dyn.s.cm⁻⁵ ($p < 0.01$) $\Delta = 31$ (12)%).

Table 3 shows the haemodynamic data measured during exercise. The values for systolic blood pressure and left ventricular end systolic volume were not significantly different during hypothyroidism and euthyroidism (176 (17) v 177 (19) mm Hg and 28 (8) v 27 (7) ml respectively). As a result, the left ventricular systolic pressure:volume ratio was not significantly affected by alterations in thyroid function (7.2 (3.5) v 7.0 (2.4) mm Hg/ml) (fig 3). The exercise ratio was above 4.0 mm Hg/ml in all patients. Pulmonary capillary wedge pressures increased with exercise to similar levels in both thyroid states (15 (4) v 17 (3) mm Hg) nor were there significant differences in left ventricular ejection fraction (75 (8) v 78 (7) %). The heart rate achieved with exercise was significantly lower during hypothyroidism (120 (18) v 137 (19) beats/min, $p < 0.02$). Cardiac output and stroke volume were also significantly lower during hypothyroidism (10.1 (1.6) v 13.2 (2.0) l/min ($p < 0.01$) and 86 (16) v 99 (21) ml

Table 3 Haemodynamic and radionuclide data during exercise in nine athyreotic patients without demonstrable cardiovascular disease when they were hypothyroid and when they were euthyroid on thyroxine replacement

Variable	Hypothyroid	Euthyroid
Heart rate (beats/min)	120 (18)	137 (19)†
Systolic blood pressure (mm Hg)	176 (17)	177 (19)
Pulmonary capillary wedge pressure (mm Hg)	15 (4)	17 (3)
Cardiac output (l/min)	10.1 (1.6)	13.2 (2.0)*
Stroke volume (ml)	86 (16)	99 (21)†
End diastolic volume (ml)	113 (17)	125 (18)†
End systolic volume (ml)	28 (8)	27 (7)
Ejection fraction (%)	75 (8)	78 (7)
Left ventricular systolic pressure:volume relation (mm Hg/ml)	7.2 (3.5)	7.0 (2.4)

Values are mean (1 SD). Differences were analysed by the Wilcoxon test for paired observations. * $p < 0.01$, † $p < 0.05$; ‡ $p < 0.02$.

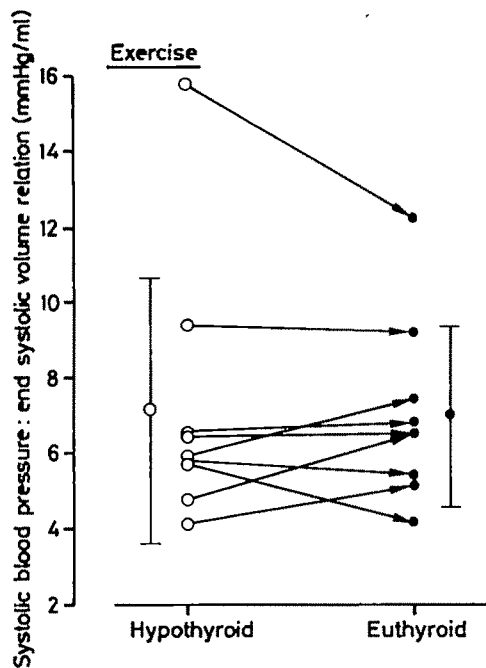


Fig 3 Individual and group mean values of the left ventricular systolic pressure: volume ratio in the hypothyroid (left) and in the euthyroid state (right) during exercise. Thyroid function had no significant effect on this variable.

($p < 0.05$) respectively). Thus at the same level of exercise, cardiac output was on average, 32 (15)% higher and stroke volume was 15 (13)% higher when the patients were euthyroid than when they were hypothyroid. End diastolic volume too was 11 (11)% higher during euthyroidism (113 (17) v 125 (18) ml ($p < 0.02$). Figure 4 shows the individual responses in cardiac output and end diastolic volume during exercise.

The increase in cardiac output with exercise was greater when the patients were euthyroid (6.1 (1.7) v 7.4 (2.0) l/min, $p < 0.02$). On average, stroke volume increased by 48 (25)% ($p < 0.01$) above the resting values when patients were hypothyroid and by 36 (28)% ($p < 0.02$) when they were euthyroid. Left ventricular end diastolic volume increased by 30 (23)% ($p < 0.01$) with exercise in hypothyroid patients. Only a non-significant trend towards higher exercise values was found in the euthyroid state ($\Delta = 20$ (24) %, $p < 0.10$). End systolic volume did not change significantly from rest to exercise in either thyroid state. During euthyroidism, a total of six out of the nine patients showed an increase in ejection fraction of at least 5% from rest to exercise, two patients had increases of $< 5\%$, and one patient had a 1% decrease in ejection fraction with exercise. All patients attained an exercise ejection fraction of at least 60%. In the hypothyroid state, seven patients had a significant increase in ejection fraction, one

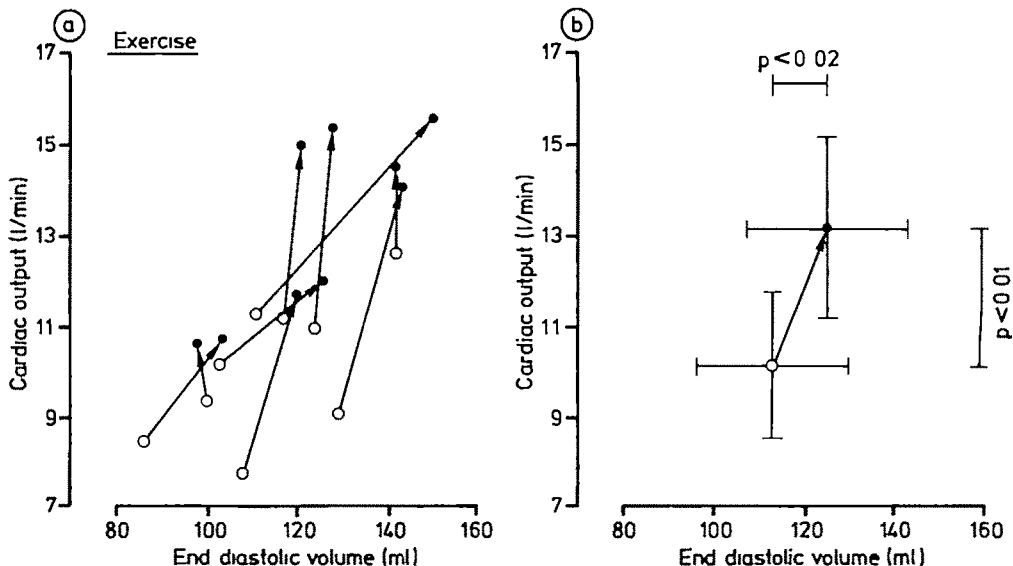


Fig 4 Relation of the left ventricular end diastolic volume with cardiac output during exercise in the hypothyroid (○) and in the euthyroid (●) state. (a) The arrows joining two points represent changes in the values for individual patients. (b) The group mean values. Left ventricular end diastolic volume and cardiac output were significantly higher when patients were euthyroid ($\Delta = 11$ (11)%, ($p < 0.02$) and $\Delta = 32$ (15)%, ($p < 0.01$) respectively).

patient had a 3% increase, and one had an 8% decrease in ejection fraction from rest to exercise. Regional wall motion was normal at rest and during exercise in all patients.

Discussion

The results of this study show that cardiac function at rest and during exercise was different in short term hypothyroidism and euthyroidism. The principal differences were decreases in end diastolic volume and stroke volume and a reduced exercise heart rate as the patients became hypothyroid. The absence of resting bradycardia in severe hypothyroidism is consistent with previous observations.^{16,17} The systolic pressure:volume ratio of the left ventricle, which was used as an estimate of the inotropic state of the myocardium, was not significantly affected by thyroid hormone deficiency. Figure 3 shows that many patients had similar exercise ratios. These data suggest that the alterations in cardiac function seen in acute hypothyroidism are primarily related to changes in loading conditions and they do not support the concept that myocardial contractility is significantly depressed by short term thyroid hormone deficiency. This view was also supported by the finding that responses in pulmonary capillary wedge pressure to exercise were consistently within normal limits when patients were hypothyroid.¹⁸ Resting and exercise cardiac output are reduced in hypothyroidism. This was explained by the low metabolic rate of the peripheral tissues.¹⁹ Furthermore, the circulating blood volume is decreased in hypothyroidism.²⁰ These factors reduce venous return to the heart and, consequently, reduce the preload on the left ventricle. An echocardiographic study by Vora *et al* showed abnormal diastolic left ventricular function in hypothyroidism,¹⁶ and this may also contribute to the decrease in end diastolic volume.

In our study thyroid function changed quickly. We do not know whether the time-action curve of the effect of thyroid hormone on the contractile state is sufficiently shortlived to prevent a bias in the results. Chronic hypothyroidism causes profound abnormalities of cardiac structure.^{21,22} Such alterations develop only after a longer period of thyroid hormone deficiency. So the results of this study are not applicable to longstanding hypothyroidism. Previous studies have also shown, however, that longterm hypothyroidism is significantly associated with large vessel coronary artery disease, which may also cause an abnormal haemodynamic state.^{23,24} A recent study by Forfar *et al* reported a reduced left ventricular ejection fraction at rest and on exercise in subjects with longstanding hypothyroidism.⁷ Their patients

had been hypothyroid for at least four months. A review of their data shows that one patient had chest pain compatible with angina and that two out of the eight patients had resting ejection fractions below 50% when euthyroid. It is conceivable that coronary artery disease contributed to the depressed left ventricular function in their patients whose mean age was 53. In contrast, our patients did not have demonstrable cardiovascular disease. They are a good study group for an analysis of the effects of acute thyroid hormone deficiency on cardiac haemodynamic function *per se*.

Fundamental to our argument that short term hypothyroidism does not significantly affect the contractile properties of the heart is the issue of whether the systolic pressure:volume ratio accurately reflects the inotropic state. Suga *et al* introduced the end systolic pressure:volume relation of the left ventricle as an estimate of myocardial contractility.^{25,26} Others have shown that the simple ratio between peak left ventricular systolic pressure and end systolic volume is also a sensitive indicator of left ventricular dysfunction.²⁷ A study by Nivatpumin *et al* suggested that in human beings this ratio is independent of load and more sensitive than the ejection fraction in detecting an impaired left ventricular function.²⁸ The use of systolic blood pressure, measured by sphygmomanometer, as an approximation of the left ventricular end systolic pressure is an obvious limitation of our study. An abnormal ratio between sphygmomanometric systolic blood pressure and end systolic volume was a sensitive indicator of an impaired left ventricular function at rest and during exercise,²⁹ we regard this ratio as a useful estimate of the inotropic state.

Studies of isolated cardiac muscle preparations and of laboratory animals showed a negative inotropic effect of thyroid hormone deficiency and an enhanced inotropic state in hyperthyroidism.³⁰⁻³² Previous human studies that used serial measurements of the systolic time intervals^{33,34} of the velocity of circumferential fibre shortening⁶ and of the radionuclide ejection fraction⁷ also suggested a reversible negative inotropic effect in chronic hypothyroidism and an enhanced contractile activity in hyperthyroidism. We do not question the validity of these studies and wish to re-emphasise that our patients cannot be used as a model of advanced primary hypothyroidism. Interpretation of these results in terms of contractile activity, however, should be done with caution. Isovolumetric and ejection phase indices are affected by several factors other than contractility and the serial evaluation of these indices can reliably indicate alterations in the inotropic state only if the loading conditions remain unchanged. The end diastolic volume may also be

decreased in chronic hypothyroidism and this may, at least in part, account for the lengthening of the pre-ejection period that is usually found in hypothyroidism without a major change in contractility.^{35,36} Similarly, the ejection fraction is intrinsically load dependent and declines with increasing afterload and decreasing preload, especially at smaller end diastolic volumes.¹¹ Previous data on the preload dependence of the velocity of circumferential fibre shortening are inconsistent and, so this index may also be difficult to interpret.^{37,38} In summary, changes in isovolumetric or ejection phase indices may not reliably reflect changes in contractility in a patient who is becoming hypothyroid. In this context it is of interest that opposing changes in preload occur when a patient becomes hyperthyroid. Merillon *et al* found that the left ventricular end diastolic volume in hyperthyroid subjects was 34% larger than in matched euthyroid controls atrially paced to the same heart rate.³⁹ The left ventricular end systolic pressure:volume ratios were similar in both groups and this suggests that alterations in contractility are of no great importance in hyperthyroidism.

Donaghue *et al* used a radionuclide method to study the effects of acute hypothyroidism on cardiac function.⁸ Their patients had been off triiodothyronine for 10 days and their mean age was 44. Overall, the resting and exercise ejection fractions were similar in both thyroid states (66 (8)% *v* 65 (6)% and 74 (10)% *v* 77 (7)%, respectively), which accords with our findings. The ejection fraction did not rise significantly with exercise in four of the nine patients when they were hypothyroid whereas all of them had a significant increase when they were euthyroid. A recent radionuclide study by Smallridge *et al* assessed the rest and exercise left ventricular ejection fraction in four hypothyroid subjects aged 20 to 48 years before treatment and after restoration of euthyroidism.⁹ Thyroid deficiency had no significant effect on the resting and exercise ejection fraction in this young adult population. This is consistent with our data. Unfortunately, those authors did not state how long the patients had been hypothyroid before the study.

This study showed that there are significant alterations in loading conditions during short term hypothyroidism. There was no evidence of a major effect of acute thyroid hormone deficiency on the contractile state of the heart.

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A comparison of sympathoadrenal activity and cardiac performance at rest and during exercise in patients with ventricular demand or atrial synchronous pacing

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SUMMARY Cardiac sympathetic function was assessed by measuring the coronary sinus overflow of noradrenaline and dopamine at rest and during supine exercise in eight patients with high degree atrioventricular block treated with dual chamber pacemakers (DDD). Patients exercised (30–60 W) during both ventricular inhibited (VVI) and atrial synchronous (VAT) pacing. During exercise cardiac output increased less markedly in the VVI mode than in the VAT mode. The cardiac output response was entirely stroke volume dependent in the VVI mode and mainly heart rate dependent in the VAT mode. Coronary sinus noradrenaline concentrations were higher in the VVI mode at rest and during exercise. Noradrenaline overflow from the heart was enhanced during VVI pacing and increased from about 100 pmol/min (17 ng/min) at rest to 1087 pmol/min during exercise (60 W) in the VVI mode and 545 pmol/min in the VAT mode. Dopamine overflow from the heart was <5 pmol/min at rest but increased 2–5 fold during exercise. Also arterial concentrations of catecholamine increased more during exercise in the VVI mode, but the differences between pacing modes were less pronounced. Circulating adrenaline seems to be of little importance for cardiac function under these conditions; in healthy individuals the arterial concentrations of adrenaline attained in this study have small effects. Cardiac noradrenaline overflow correlated with pulmonary capillary venous pressures and atrial rates in both pacing modes, indicating a relation between cardiac sympathetic activity and cardiac function.

Enhanced cardiac release of noradrenaline may increase cardiac contractility and thereby partially compensate for the lack of heart rate responsiveness to exercise during VVI pacing.

The beneficial haemodynamic effects of dual chamber pacing (VAT, VDD, DDD) with preserved atrioventricular synchrony and rate responsiveness compared with ventricular demand pacing (VVI) at a constant heart rate are well documented.^{1–5} A recent study also suggests that the prognosis of patients with atrioventricular block may be more favourable with dual chamber pacing than with VVI pacing.⁶ When the heart is paced at a constant rate, cardiac output

can only increase by a change in stroke volume, caused by increased contractility or by Starling mechanisms, brought about by enhanced venous return.

Sympathetic nerve activity helps to regulate heart rate and contractility in the normal and failing heart.^{7,8} Circulating adrenaline may contribute to the regulation of cardiac function, since small increases in arterial adrenaline concentrations can elicit mainly stroke volume dependent increases of cardiac output in human beings.⁹ Sympathoadrenal mechanisms have been implicated in the cardiac adaptation to exercise under different pacing conditions,^{4,5} but cardiac sympathetic nerve activity and circulating

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concentrations of catecholamine have not, to our knowledge, been measured during exercise in individuals on different pacing modes.

Plasma concentrations of noradrenaline are considered to be a good indicator of sympathetic nerve activity¹⁰ and several studies of plasma concentrations of noradrenaline in the peripheral venous system have been performed to assess sympathetic activity in relation to cardiac function.¹¹ Heart failure is associated with raised concentrations of noradrenaline in venous plasma at rest and during exercise.¹²⁻¹⁴ Sympathetic nerve activity, however, is not uniformly regulated and may vary considerably between organs, and responses to various kinds of stress may also vary considerably between organs.¹⁵ The heart contributes only about 3% of the noradrenaline in arterial plasma.¹⁶ About half of the noradrenaline in antecubital venous plasma is derived from the forearm tissues and stress may influence sympathetic activity in these peripheral tissues and the heart quite differently.¹⁷ Similarly, Fischer Hansen *et al* estimated that approximately half of the noradrenaline measured in coronary sinus plasma was derived from the heart.¹⁸ Therefore, it seems reasonable that cardiac sympathetic nerve activity should be assessed in terms of noradrenaline overflow from the heart rather than by measurements of noradrenaline concentrations in peripheral venous plasma.^{19,20}

The present study was undertaken to evaluate the roles of cardiac sympathetic nerve activity and circulating catecholamines in patients with complete heart block treated with dual chamber pacemakers. Catecholamine concentrations in arterial plasma and the coronary sinus overflow of noradrenaline were measured at rest and during exercise with the pacemakers programmed in the atrial synchronised mode (VAT) or the ventricular inhibited mode (VVI) (that is at a constant heart rate).

Patients and methods

PATIENTS

We studied eight patients (seven men) aged 66–80 (mean 74) years. They had been treated with DDD pacemakers for a mean of 26 (range 2–96) months because of symptomatic high degree atrioventricular block of unknown aetiology. Two patients had clinical signs of heart failure; one of them had slight to moderate incompetence of the aortic valve. One patient had effort angina. Table 1 shows some clinical data including exercise capacities in the sitting position. Informed consent was obtained and the study was approved by the ethics committee of the Karolinska Hospital.

PROCEDURE

The patients underwent two exercise tests in the supine position. They rested for an hour between tests. The pulse generator was randomly programmed for VAT or VVI pacing about an hour before catheterisation. Four of the patients were studied in the VAT mode first. After we had completed the investigation in the first selected mode we programmed the pulse generator to the other mode.

All patients underwent cardiac catheterisation after premedication with diazepam (5 mg). A Swan-Ganz catheter was inserted percutaneously under local anaesthesia into an antecubital vein and positioned in the pulmonary artery under fluoroscopic guidance. A thermodilution catheter was inserted by a similar technique via the antecubital vein on the other arm and positioned in the coronary sinus. A short Teflon catheter was introduced into the right brachial artery. The catheters were connected to electromechanical transducers. The pressures were registered on a Mingograph (Sicor) and the values were processed in a computer (IBM 1800). The mid-

Table 1 Clinical data and symptom limited exercise capacity in patients in the sitting position during pretrial tests in the VVI and VAT modes

Case No	Age	Sex	BSA* (m ²)	Heart volume (ml/m ²)	Exercise capacity (W)		Other relevant disease	Medication
					VVI	VAT		
1	77	M	1.76	500	120	130	Aortic incompetence Congestive heart failure	Digoxin 0.25 mg × 1 Furosemide 40 mg × 2 Potassium chloride
2	67	M	1.86	500	85	90		
3	74	M	1.82	460	100	120		
4	76	M	1.82	360	130	140	Angina pectoris	Furosemide 40 mg × 1 Potassium chloride Digoxin 0.13 mg × 1 Furosemide 40 mg × 1
5	80	M	1.70	450	100	115		
6	75	M	1.88	560	100	110		
7	66	F	1.64	500	90	100		
8	76	M	2.00	500	85	100		

*Body surface area

thoracic level was taken as zero reference level for pressures. Systemic vascular resistance was calculated as the mean brachial artery pressure divided by cardiac output. Cardiac output was determined by the direct Fick method. Ventilation and oxygen uptake were measured with a ventilation monitor and an argon dilution technique (Bourns Inc, Model Ls 75), which were checked regularly against a dynamic pneumotachograph calibrator. Inspired and expired air was analysed on line for oxygen, carbon dioxide, nitrogen, and argon by a mass spectrometer (20th Century Electronics, Model 200 Mga) calibrated with a gas mixture analysed by the Scholander technique. Oxygen consumption reached a plateau on each work load. We measured coronary blood flow by the continuous thermodilution technique after injection of an isotonic saline solution at room temperature.²¹ We used the mean of 2–4 measurements to calculate coronary blood flow.

Measurements were performed and blood was sampled with the patient supine at rest with both legs placed on the pedals 15 cm above the table and during the sixth minute of exercise at the work load 30 W. If possible, patients completed an additional work period at 60 W. At the end of each steady state condition, blood samples were drawn simultaneously from the coronary sinus and the brachial artery to measure plasma catecholamines. To assess coronary sinus noradrenaline overflow, we measured coronary blood flow before and after taking each blood sample.

Samples of blood (10 ml) were collected in ice-cold centrifuge tubes containing ethylene diaminetetraacetic acid to give a final concentration of 10 mmol/l. After centrifugation at +4°C, plasma was removed and stored at –80°C until analysis. Plasma concentrations of noradrenaline, adrenaline and dopamine were measured by high performance cation exchange liquid chromatography with electrochemical detection.^{22,23} The assay has a sensitivity of <0.05 nmol/l and inter and intra assay coefficients of variation of 9–12% at 0.1–0.2 nmol/l (that is basal adrenaline and dopamine concentrations) and 2–3% above 1 nmol/l (that is basal noradrenaline concentrations) and has been validated.²³ In one case adrenaline was not measured because of interference in the assay. In another case a couple of test tubes were broken during centrifugation.

Coronary plasma flow was calculated from individually determined haematocrit values. Noradrenaline overflow from the heart was calculated as the difference between plasma concentrations of noradrenaline in the coronary sinus and the arterial plasma multiplied by coronary sinus plasma flow. To correct for the removal of noradrenaline from arterial plasma by the heart, we calculated the extraction of endogenous adrenaline, which can be

used to assess the extraction of noradrenaline^{20,24,25} and dopamine²⁵ in an organ. Thus a "corrected" difference in the plasma concentration of noradrenaline over the heart was multiplied by the coronary sinus plasma flow. This gives a better estimate of the true organ contribution to the noradrenaline overflow in the coronary sinus—that is the local sympathetic nerve activity.

Results are presented as mean values (SEM). Statistical analyses were performed by three factor analysis of variance (ANOVA) and by linear regression analysis by the least squares method.

Results

All eight patients completed exercise at 30 W but only six patients managed to exercise for six minutes at 60 W. The mean (SD) exercise capacities of patients in the sitting position (table 1) were higher during VAT pacing than during VVI pacing (113 (17) v 101 (16) W; $p < 0.001$).

HAEMODYNAMIC VARIABLES

Figures 1 and 2 show the haemodynamic data. With VVI pacing the mean (SEM) ventricular heart rate did not change during exercise (70 beats/min), whereas atrial rate increased from 76 (5) to 118 (7) beats/min. The atrial rate was lower during VAT pacing ($p < 0.01$) both at rest and during exercise. It increased from 65 (4) to 103 (5) beats/min at the highest work load (fig 1). None of the patients had ventriculoatrial conduction during VVI pacing. Stroke volumes were 61 (3) ml in the VVI mode and 71 (5) ml in the VAT mode ($p < 0.05$) at rest and increased by 69% ($p < 0.001$) and 23% (NS by ANOVA) respectively during exercise. The difference in stroke volume response, as shown by the interaction term of the ANOVA, was significant ($p < 0.001$). The resulting values for cardiac output tended to be lower in the VVI mode at rest and were significantly lower during exercise (for example 6.1 (0.2) v 7.3 (0.3) l/min at 30 W; $p < 0.01$; fig 1). During VVI pacing cardiac output increased significantly less in response to exercise ($p < 0.001$ by ANOVA). Oxygen consumption was similar in the two pacing modes both at rest and during exercise (with increases from approximately 250 to 1000 ml at standard temperature and pressure (dry) per minute in both modes). Consequently, the arteriovenous oxygen concentration differences were significantly (about 10–15%) larger throughout the experiments in the VVI mode ($p < 0.001$ by ANOVA; fig 1). Coronary blood flow increased during exercise, but these values were similar for the two pacing modes (fig 2). Systolic blood pressure was not different in the two pacing modes either at rest or during exercise

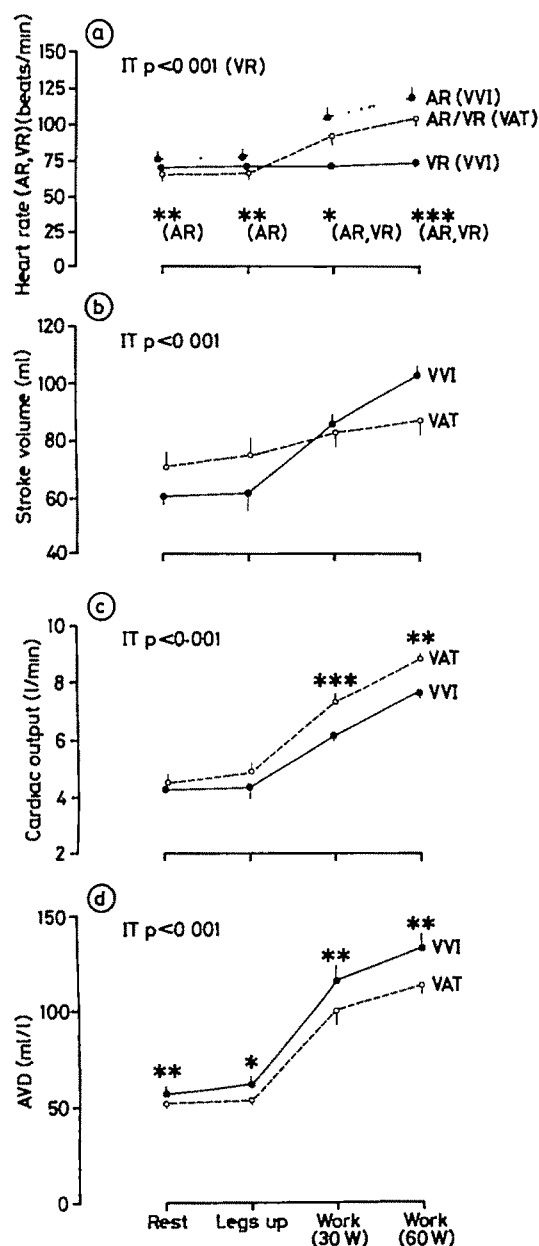


Fig 1 Mean values (SEM) for heart rate (atrial (AR) and ventricular (VR)), stroke volume, cardiac output, and arteriovenous oxygen concentration difference (AVD) during VVI or VAT pacing. AR and AVD were significantly higher throughout the experiments during VVI pacing ($p < 0.001$ by ANOVA). The figure shows the p values (** < 0.01 and *** < 0.001) when the two pacing conditions were compared at individual time points after the ANOVA had shown differences for the variable. Significance levels are given when the interaction term (IT) indicated that changes over time differed between pacing modes.

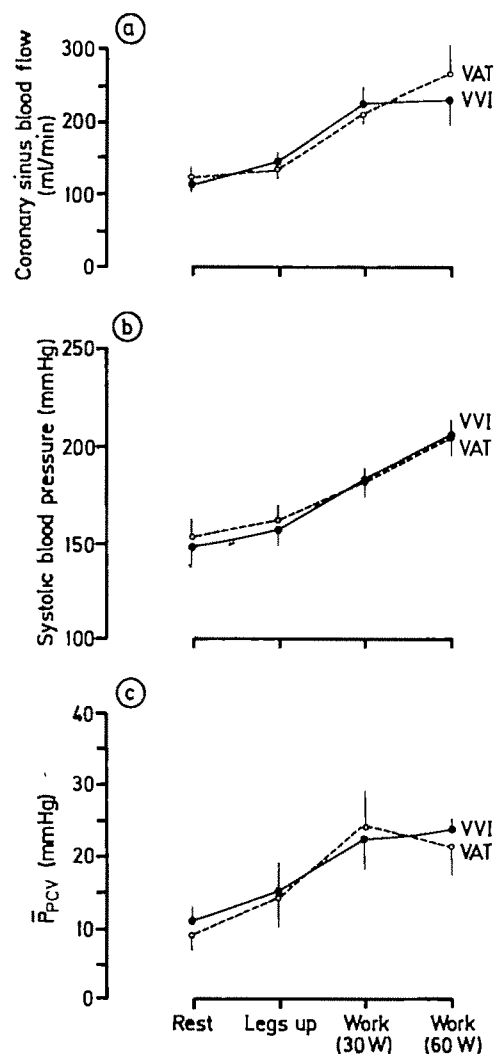


Fig 2 Coronary sinus blood flow, systolic blood pressure, and pulmonary capillary venous pressure (P_{pcv}). See legend to fig 1 for symbols.

(fig 2). During exercise diastolic blood pressure increased in the VAT mode (from 75 (3) to 92 (5) mm Hg; $p < 0.001$) but not in the VVI mode. These responses differed significantly ($p < 0.001$ by ANOVA). Mean arterial blood pressure was similar at rest for both modes but increased more during exercise in the VAT mode (for example 127 (5) v 119 (6) mm Hg, $n = 8$, at 30 W; $p < 0.01$). Systemic vascular resistance was reduced during exercise ($p < 0.001$) and tended to be approximately 10–15% lower in the VAT mode, but the difference between modes was not significant.

Pulmonary arterial pressures were similar in the

Table 2 Mean (SEM) catecholamine concentrations in arterial (A) and coronary sinus (CS) plasma ($n = 6-8$), adrenaline extraction by the heart ($n = 5-7$), and corrected noradrenaline and dopamine overflow from the heart ($n = 5-7$).

	Noradrenaline (nmol/l)		Adrenaline (nmol/l)		Dopamine (nmol/l)		Adrenaline extraction (%)	Nor-adrenaline overflow (pmol/min)	Dopamine overflow (pmol/min)
	CS	A	CS	A	CS	A			
Resting:									
VVI	3.93 (0.81)	2.64 (0.50)	0.17 (0.04)	0.25 (0.07)	0.16 (0.02)	0.13 (0.02)	29 (4)	141 (46)	3.4 (1.7)
VAT	3.14 (0.66)*	2.18 (0.41)	0.14 (0.04)	0.20 (0.07)*	0.12 (0.02)*	0.14 (0.04)	22 (8)	109 (45)	2.8 (1.7)
Legs up:									
VVI	3.08 (0.36)	2.62 (0.59)	0.18 (0.03)	0.28 (0.06)	0.15 (0.02)	0.13 (0.03)	31 (6)	112 (30)	4.6 (1.5)
VAT	2.50 (0.34)*	1.99 (0.29)	0.17 (0.04)	0.23 (0.06)*	0.10 (0.01)***	0.11 (0.02)	25 (4)	82 (24)	-0.2 (1.6)
Work (30 W):									
VVI	14.82 (5.25)	5.75 (0.54)	0.35 (0.10)	0.42 (0.08)	0.35 (0.12)	0.20 (0.03)	18 (9)	565 (79)	4.7 (3.2)
VAT	8.87 (2.94)**	3.83 (0.43)*	0.27 (0.05)	0.30 (0.07)	0.21 (0.06)**	0.13 (0.02)	0 (8)	271 (131)*	5.8 (3.0)
Work (60 W):									
VVI	18.35 (2.95)	9.80 (1.56)	0.61 (0.19)	0.71 (0.16)	0.44 (0.07)	0.29 (0.04)	6 (5)	1087 (265)	23.9 (7.9)
VAT	11.07 (1.80)**	7.49 (1.46)	0.49 (0.12)	0.56 (0.11)	0.24 (0.04)*	0.17 (0.02)	12 (11)	545 (139)*	11.5 (4.5)
Differences between VVI and VAT in 3 factor ANOVA	p < 0.01	p < 0.05		p < 0.05	p < 0.01				
Significance of IT in 3 factor ANOVA	p < 0.001				p < 0.01	p < 0.05		p < 0.01	

Two patients could not exercise at a work load of 60 W. In one patient adrenaline concentrations could not be analysed because of interference. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for 2 factor analyses (VVI v VAT) performed at different time points after the 3 factor ANOVA had shown significant differences. A significant interaction term (IT) indicates differences between VVI and VAT modes (that is a difference in the slope of the curve) in the change of a variable over time. Significant effects over time (that is an effect of work) were seen for all variables.

two pacing modes (for example 25(3)/12(3) mm Hg at rest and 49(6)/25(5) mm Hg at 30 W in the VAT mode). Right atrial mean pressure increased two to three fold from 5 (1) mm Hg in both pacing modes and tended to be higher ($p < 0.1$ by ANOVA) during VVI pacing. Pulmonary capillary venous pressures varied considerably between patients, but values were similar within patients in the two pacing modes both at rest and during exercise (fig 2).

CATECHOLAMINES

Concentrations of noradrenaline, adrenaline, and dopamine in arterial plasma at rest and during exercise were higher in the VVI mode (table 2). Increases in arterial plasma noradrenaline induced by exercise were considerably larger than those in adrenaline and dopamine, but analysis of variance showed that these increases were not significantly different. At rest the heart extracted approximately 25–30% of circulating adrenaline in both pacing modes (table 2). During exercise the cardiac extraction of adrenaline fell to about 10% (NS). Plasma concentrations of noradrenaline in the coronary sinus were higher than the arterial concentrations both at rest and during exercise. There were large inter-individual variations in coronary sinus noradrenaline concentrations during exercise (for example 3.33–50.0 nmol/l at 30 W in the VVI mode). Concentrations of noradrenaline in the coronary sinus were, however, consistently higher during VVI than dur-

ing VAT pacing (table 2). Also plasma dopamine concentrations in the coronary sinus were higher than the arterial concentrations and increased significantly ($p < 0.01$) during exercise (table 2). They were higher during VVI pacing both at rest and during exercise ($p < 0.01$; table 2) and they increased more in the VVI mode (table 2).

Coronary sinus noradrenaline overflow tended to be greater at rest and was twice as large in the VVI mode as in the VAT mode during exercise (table 2, fig 3). Cardiac noradrenaline overflow responses to exercise were significantly enhanced during VVI pacing ($p < 0.01$ by ANOVA). Dopamine overflow was less than 5% of the noradrenaline overflow into the coronary sinus both at rest and during exercise and in both pacing modes. Dopamine overflow from the heart did increase ($p < 0.01$) during exercise and again the response during VVI pacing tended to be larger than that seen during VAT pacing (table 2, fig 3). The difference in dopamine overflow was, however, not significant. In the calculations of noradrenaline and dopamine overflow shown in table 2, the removal of catecholamines from arterial plasma by the heart was assessed by the cardiac extraction of adrenaline, in order to obtain a more accurate measure of the cardiac contribution to noradrenaline and dopamine in the coronary effluent (see methods). In a few instances concentrations of adrenaline in the coronary sinus were slightly higher than in the arterial concentrations. Catecholamine extraction by

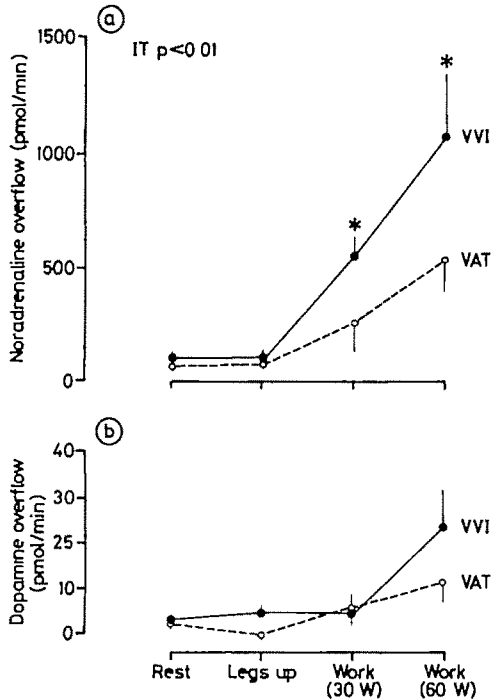


Fig 3 Noradrenaline and dopamine overflow into coronary sinus plasma. Catecholamine overflow values were corrected (according to adrenaline extraction) for the removal of catecholamines from arterial plasma by the heart. Only paired observations (where results were obtained from each patient under both pacing conditions) are given. See table 2 and results for three factor ANOVA analyses (* $p < 0.05$ for differences between VVI and VAT)

the heart was then considered to be 0%. Results and conclusions about noradrenaline overflow were, however, similar even if adrenaline extraction was said to be <0% (in fact the difference between pacing modes became slightly larger) or if cardiac catecholamine extraction was not taken into account at all. VVI pacing was clearly associated with enhanced noradrenaline overflow into the coronary sinus.

CORRELATIONS

Plasma concentrations of noradrenaline in the coronary sinus were significantly correlated with atrial rate (fig 4), as were cardiac noradrenaline overflow values during VVI ($r = 0.78$, $p < 0.001$) and during VAT ($r = 0.69$, $p < 0.001$) pacing. Pulmonary capillary venous pressures were correlated with noradrenaline concentrations in coronary sinus plasma and noradrenaline overflow from the heart both at rest and during exercise. Pooling of VVI and VAT pacing values, because the study group was so small, gave the following correlation coefficients: pulmonary capillary venous pressure v noradrenaline concentrations at rest ($r = 0.51$, $n = 16$, $p < 0.05$), noradrenaline overflow at rest ($r = 0.79$, $n = 13$, $p < 0.01$), noradrenaline concentrations at 30 W ($r = 0.75$, $n = 14$, $p < 0.01$), and noradrenaline overflow at 30 W ($r = 0.65$, $n = 11$, $p < 0.05$). These correlations were generally stronger in the VVI mode than in the VAT mode, but the numbers were too small for valid analysis.

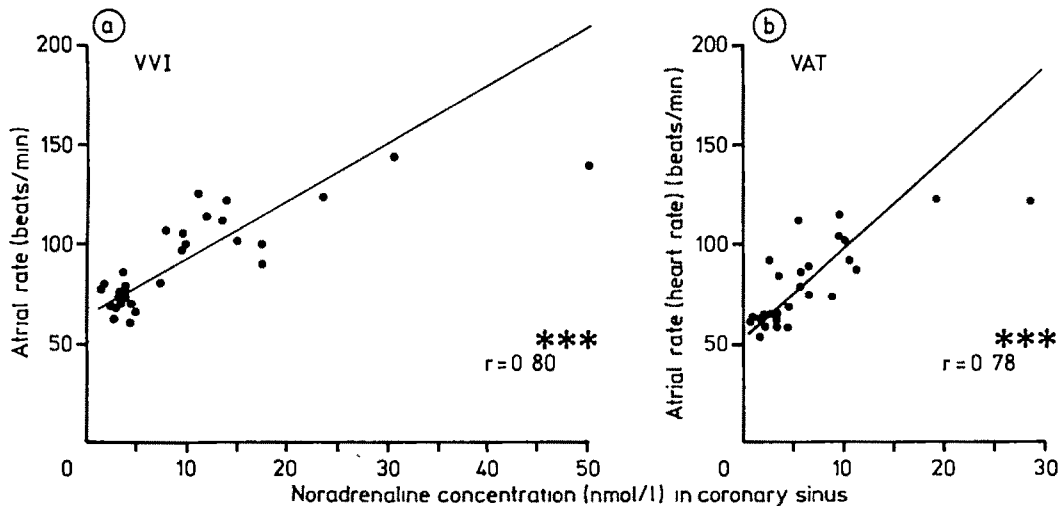


Fig 4 Correlations between noradrenaline concentrations in coronary sinus plasma and atrial rate during VVI pacing (a) and heart rate during VAT pacing (b). Similar relations were found between these variables and cardiac noradrenaline overflow values (see text) *** $p < 0.001$

Discussion

The present investigation confirms previous observations¹⁻⁵ that cardiac output is improved during exercise when VAT pacing allows heart rate to increase in response to the sinus node activity. The lack of ventricular rate responsiveness during VVI pacing is partially compensated for by an increased stroke volume response to exercise. The proposed explanation for the high atrial rate seen during exercise with VVI, as compared with VAT pacing (references 3 and 4 and present results) is an increase in sympathetic nerve activity. Indeed, an enhanced cardiac sympathetic response to exercise in the VVI mode would be a most appropriate way to increase contractility when demands on increased stroke volume are high.⁶ The present data clearly demonstrate that cardiac sympathetic nerve activity is enhanced during VVI pacing, especially when demands are increased by exercise. Thus coronary sinus noradrenaline concentrations and cardiac noradrenaline overflow values were higher in this pacing mode. It is noteworthy that the enhancement of sympathetic activity seen during VVI, as compared with VAT pacing, was greater in the heart than in the rest of the body. So cardiac noradrenaline overflow increased more markedly than arterial noradrenaline concentrations (by 404 *v* 119% at 30 W) during exercise in the VVI mode. Similarly, the enhanced atrial rate response to exercise was not accompanied by enhanced blood pressure or oxygen consumption in response to exercise during VVI, as compared with VAT pacing. Cardiac sympathetic nerve activity seems to be more closely related to cardiac demands than to sympathetic nerve activity in the rest of the body.

How well does coronary sinus noradrenaline overflow reflect cardiac sympathetic nerve activity? Animal studies have shown a frequency dependent overflow of noradrenaline from the heart during stimulation of the sympathetic cardiac nerves,²⁶⁻²⁸ and correlations between increases in myocardial contractility and noradrenaline overflow.^{26,28} Coronary vasodilatation or mechanical factors associated with myocardial contractions or both may facilitate noradrenaline diffusion into coronary sinus plasma, as has been shown in high frequency pacing.²⁹ It is, however, unlikely that such a difference in noradrenaline diffusion could explain our pacing results because noradrenaline overflow was highest during fixed rate pacing. Furthermore, blood flow in the coronary sinus was similar in the two pacing modes both at rest and during exercise. Though direct techniques cannot be used in patients to verify that coronary sinus noradrenaline overflow mirrors cardiac sympathetic nerve activity in humans, the

present findings of clear-cut correlations between atrial rates and cardiac noradrenaline overflow in both pacing modes support the contention that coronary sinus noradrenaline overflow does reflect cardiac sympathetic nerve activity.

The exercise induced increases in arterial plasma adrenaline concentrations were considerably smaller than the increases in cardiac noradrenaline overflow. Cardiac sympathetic nerve activity was probably the dominating sympathoadrenal factor influencing cardiac function in the present study, because neurogenic mechanisms usually are more important than circulating catecholamines in the control of heart function^{7,15} and the arterial adrenaline concentrations attained in the present study were low. For example, an increase in arterial plasma adrenaline concentrations to 1.3 nmol/l by intravenous infusion increased the heart rate by only 5 beats/min and stroke volume by 10% in healthy volunteers.⁸ The only patient in the present study with adrenaline concentrations > 1.3 nmol/l during exercise had a simultaneously determined coronary sinus noradrenaline overflow of 2026 pmol/min—that is the highest value recorded. Thus it is reasonable to assume that circulating adrenaline was of little importance in the cardiac adaptation to exercise in the different pacing modes.

Adjustments of the peripheral circulation to exercise are important to cardiac function, because afterload and venous return are important determinants of stroke volume.⁷ For example during low level exercise Frank-Starling mechanisms increased stroke volume in denervated hearts of heart transplant recipients.³⁰ In the present study the increase in arterial concentrations of noradrenaline induced by exercise tended to be higher during VVI pacing. This might reflect increased activity of peripheral vasoconstrictor nerves and may be associated with venoconstriction and enhanced venous return. Even though right atrial mean pressures tended to be higher in the VVI mode during exercise, we cannot tell from the present data whether this contributed to the enhanced response of stroke volume to exercise during VVI pacing because ventricular volumes were not monitored.

We have, so far, no reference material comprised of healthy individuals. The patients in the present study were old and had impaired cardiac function, as indicated by low cardiac output values and high wedge pressures during supine exercise. Previous studies have shown that heart failure is associated with high concentrations of venous noradrenaline in the forearm at rest^{11,12,14} and inappropriately large increases in venous plasma noradrenaline concentrations in response to exercise.¹³ For reasons mentioned in the Introduction, these changes in noradrenaline

concentrations should be regarded as indirect measures of cardiac function (that is compensatory changes in the activity of peripheral vasoconstrictor nerves) rather than measures of cardiac sympathetic nerve activity. Cardiac noradrenaline overflow in heart failure is increased at rest.¹⁹ The cardiac noradrenaline overflow values found in the present study (approximately 100 pmol/min or 17 ng/min at rest) were in between the values reported for healthy control and patients with heart failure at rest (that is, 5 and 32 ng/min, respectively) in the radiotracer infusion study of Hasking *et al.*¹⁹ Interestingly, we saw significant correlations between pulmonary capillary venous pressures and coronary sinus concentrations of plasma noradrenaline or cardiac noradrenaline overflow both at rest and during exercise. Thus our data support the ideas that demands influence cardiac sympathetic nerve activity and that cardiac, as well as peripheral sympathetic nerve activity is enhanced when cardiac function is compromised. In fact, the results of Hasking *et al.*¹⁹ and those of the present study indicate that the increase in compensatory sympathetic nerve activity is largest in the target organ, which emphasises the importance of regional studies of noradrenaline overflow in pathophysiological and physiological studies.

Dopamine overflow from the heart was very small in relation to noradrenaline overflow. Pharmacological doses of exogenous dopamine have well-known cardiostimulatory effects³¹ and failing human hearts contain relatively high concentrations of dopamine.³² It has been suggested that dopamine is immediately conjugated to sulphate upon release in the tissues and that concentrations of conjugated dopamine would reflect dopamine release better than free dopamine concentrations in plasma.³³ This is, however, not the case in the canine kidney after sympathetic nerve stimulation.³⁴ Furthermore, renal extractions of noradrenaline and dopamine from plasma are equally large³⁵ and the renal venous overflow of dopamine is even larger in relation to noradrenaline overflow than would be expected on the basis of the tissue contents of noradrenaline and dopamine.³⁴ Thus free dopamine overflow from a tissue, as assessed in the present study, should reflect release of dopamine in the tissue. In our experience dopamine overflow is proportionally greater into renal venous plasma in the dog,³⁴ and in human beings.³⁵ The present results therefore indicate that dopamine release is very small in relation to noradrenaline release and probably only represents release of precursor dopamine stored in noradrenergic nerves in the human heart. It is doubtful whether this dopamine is physiologically important.

It has been proposed that increased cardiac

turnover of catecholamines would accelerate the disease process in heart failure by reducing cardiac β adrenoceptor sensitivity.³⁶ Increased sympathetic nerve activity would also be expected to increase myocardial oxygen requirements and cardiac work,^{6,7} which eventually might lead to deterioration of already compromised hearts. The present findings of enhanced sympathetic responses to exercise and correlations between cardiac noradrenaline overflow and function are of particular interest in view of the indications⁶ that the prognosis is less good in patients with congestive heart failure on VVI pacing than on VAT pacing.

The finding that impaired adaptation to exercise during VVI pacing was accompanied by enhanced noradrenaline overflow indicates that VVI pacing at a constant heart rate is associated with enhanced activity of the cardiac sympathetic system. Dopamine release in the heart and circulating adrenaline seem to be less important than cardiac sympathetic nerve activity for the adaptation to exercise under the reported conditions. The enhanced cardiac sympathetic nerve activity during constant rate (VVI) pacing may well have adverse effects on failing or ischaemic hearts and may influence the clinical course of such patients.

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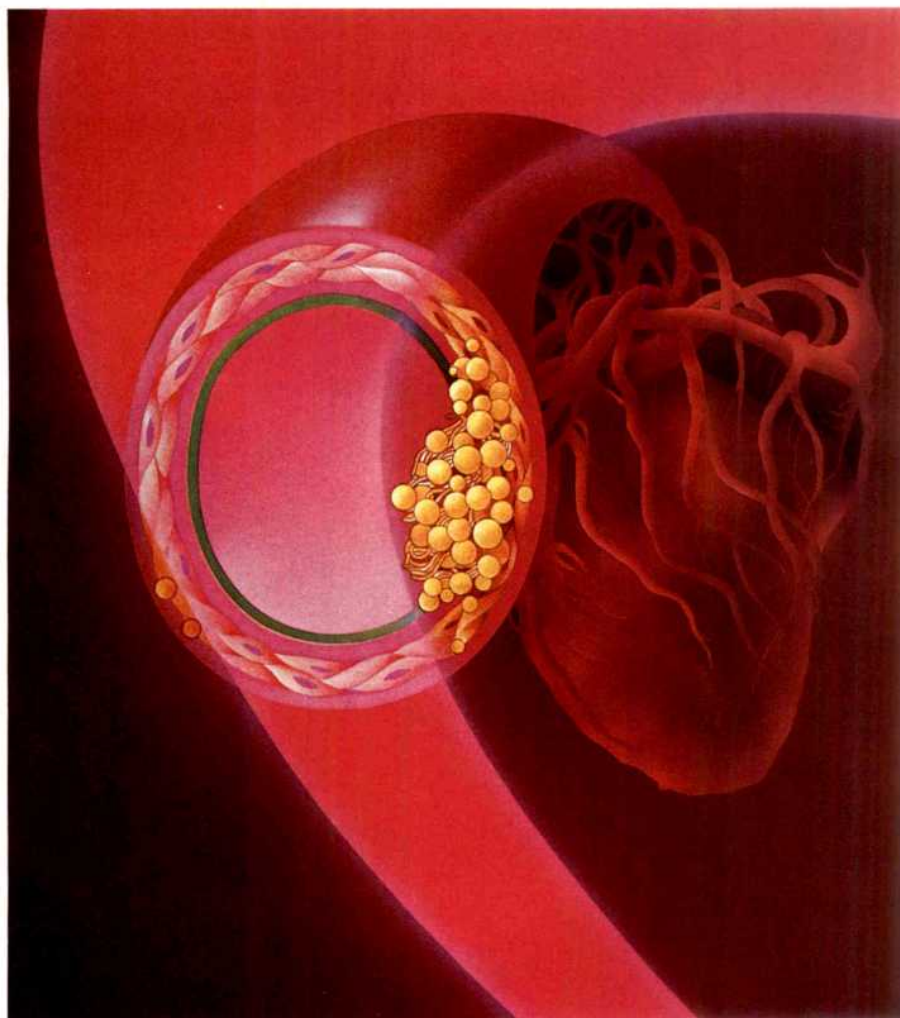
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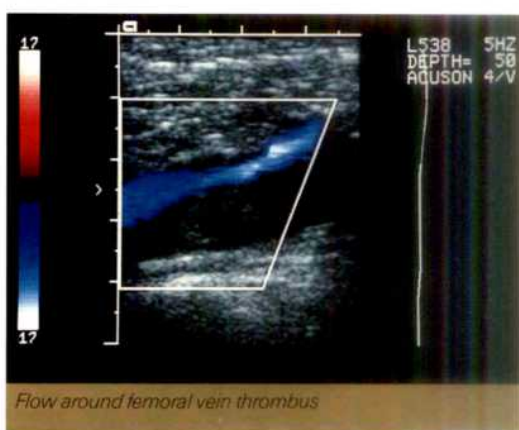
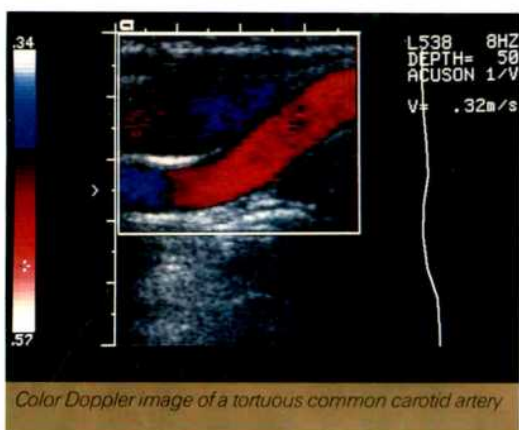
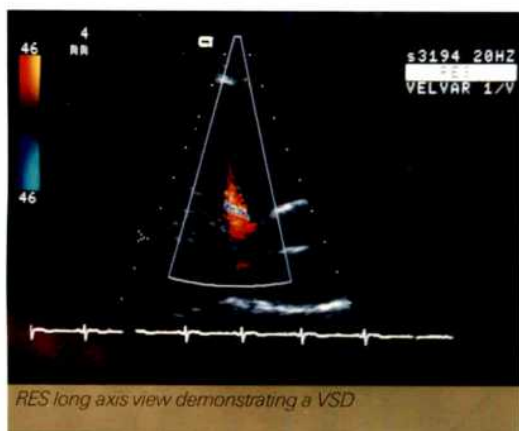


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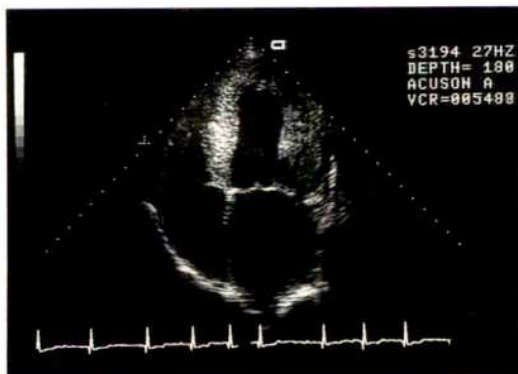
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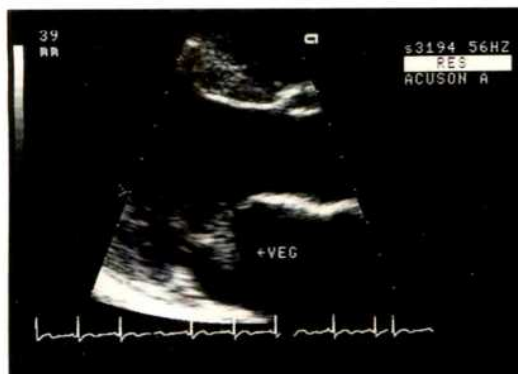
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Apical four chamber view illustrating detail resolution and myocardial tissue texture differentiation



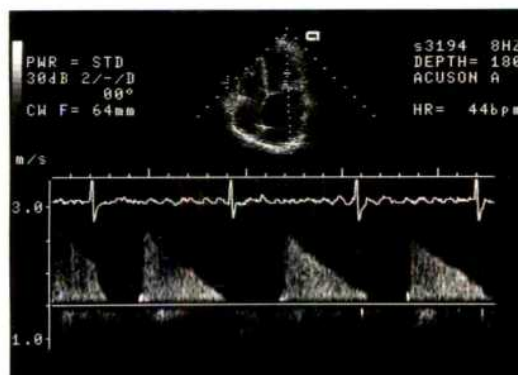
Apical five chamber view demonstrating aortic insufficiency (Mosaic Pattern)



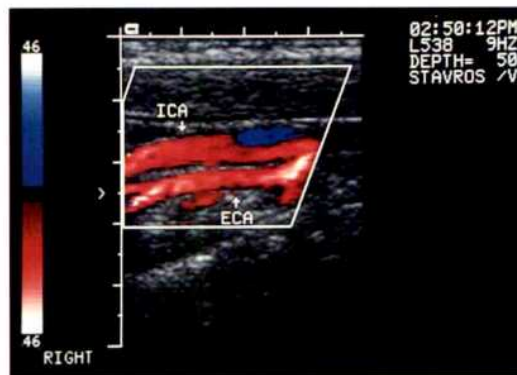
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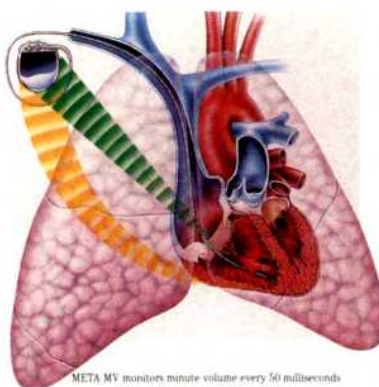
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Measurements of the dimensions of the aortic and pulmonary pathways in the human fetus: a correlative echocardiographic and morphometric study

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SUMMARY Thirty normal hearts from fetuses aborted at 10–33 weeks' gestation were measured directly and the results were compared with echocardiographic measurements in 20 normal live fetuses of 23–27 weeks' gestation. The diameters of the aorta, aortic isthmus, pulmonary arteries, and arterial duct were measured at standard levels and expressed as a ratio of the diameter of the ascending aorta. The ratios for the isthmus, the duct, and the right pulmonary artery were: 0.63 (0.11), 0.51 (0.13), 0.56 (0.10) respectively for the direct measurement and 0.73 (0.07), 0.7 (0.08), 0.62 (0.06) respectively at echocardiography. These results show that in mid-gestation the isthmus of the human fetus is not as small as that reported in animal models. This indicates that the distribution of the fetal circulation may not be the same either.

Our present knowledge of fetal circulation is derived mainly from studies carried out on animal models, particularly in lambs. Few studies have been performed in human fetuses.¹⁻³ The experimental procedures used to study the lamb may have affected the physiological patterns. Studies were first performed on exteriorised fetal animals⁴⁻⁷ and, subsequently, in utero.^{8,9} The results of these studies led to the "flow theory", which directly relates the capacity of blood vessels to their relative sizes.¹⁰ This relation was subsequently extended as the "flow-dependence rule"¹¹ which hypothesised that, if the capacity of blood vessels is directly related to their cross sectional area, the sum of the squared diameters of the arterial branches should be equal to the square of the diameter of the arterial stem itself.

These haemodynamic indices of the fetal circulation derived from studies in animals have subsequently been extensively extrapolated to the human fetus, with adjustment only for the greater proportion of blood received by the human brain. In

this way, it has been calculated that the diameter of the human aortic isthmus is only about seven tenths that of the remainder of the aorta. It has further been presumed that the isthmal segment of the aortic arch is considerably narrower than the arterial duct (ductus arteriosus) and that the pulmonary arteries themselves are narrower still. Recent echocardiographic observations during mid-gestation on developing and normal human fetuses in our laboratories, however, suggest that the dimensions of

Table Age distribution of the fetuses studied

Weeks of gestation	Necropsy	Echocardiography
10	2	
14	3	
15	1	
16	2	
17	3	
18	3	
20	6	
21	1	
23	5	2
24		9
25		6
26	1	2
27		1
33	1	
Unknown	2	

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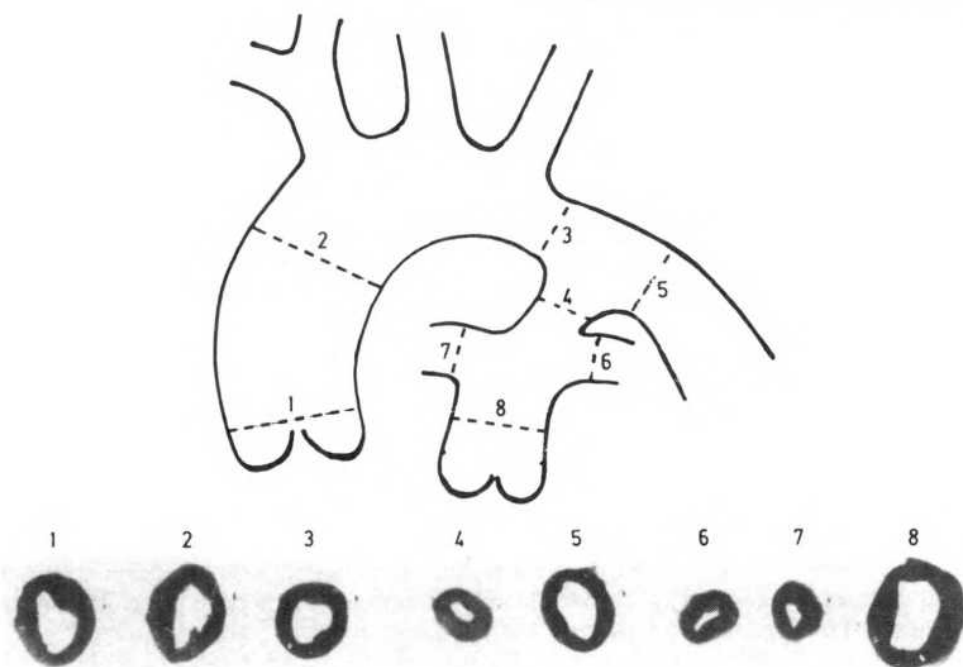


Fig 1 Levels of the arterial pathways at which the luminal diameters were assessed. The corresponding slices are shown below. (1) ascending aorta, (2) ascending aorta before the origin of the brachiocephalic artery, (3) isthmus, (4) arterial duct, (5) descending aorta, (6) left pulmonary artery, (7) right pulmonary artery, (8) pulmonary trunk.

the isthmus and pulmonary arteries are considerably greater than would be assumed according to the flow hypothesis that is based on measurements taken in fetal lambs. To investigate further this potential discrepancy, we performed echocardiographic and postmortem morphometric studies of the diameters of the aortic and pulmonary arterial pathways in two groups of normal human fetuses.

Patients and methods

ABORTED FETUSES

We studied the hearts and great vessels of 30 normal human fetuses after cardiovascular abnormalities were excluded at necropsy. The gestational age ranged from 10 to 33 weeks; in most it was 10 to 23 weeks (table). Because the drugs used to induce abortions may affect the wall of the arterial duct we studied only fetuses that had aborted spontaneously. The great vessels were separated from the heart and lungs. Twenty seven specimens were assessed after fixation in a 4% formaldehyde solution for at least 24 hours. The other three specimens were assessed both before and after fixation. We cut 300 μ m thick slices of each specimen at standard levels of the arterial

pathways (fig 1). The slices were examined under a light microscope connected to a BBC computer and a graphics table. We used this apparatus to measure the perimeters of the lumens. The luminal diameters

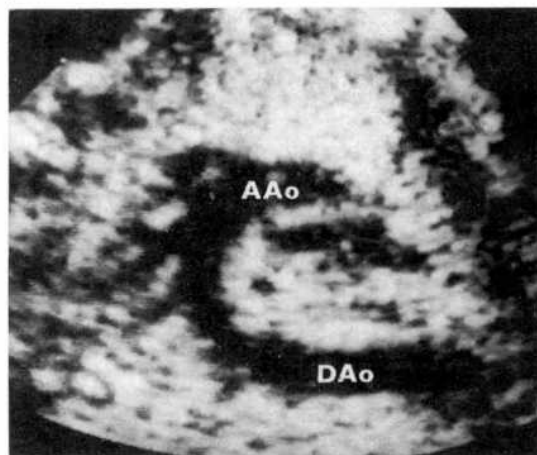


Fig 2 Echocardiogram (long axis view of the aortic arch) showing the uniform dimension of the aortic arch with only a minimal narrowing at the site of the isthmus. AAo, ascending aorta; DAo, descending aorta.



Fig 3 Echocardiogram (short axis view of the great arteries) showing the size of the arterial duct (duct) and the pulmonary trunk (mpa). ao, aorta; rpa, right pulmonary artery; s, spine.

were then derived by assuming that the vessels were circular in cross section. We took the mean of two measurements. Because the size of the specimens varied, we calculated the ratio between the diameter of each vessel and that of the ascending aorta. We chose the ascending aorta as the "control" so that we could compare postmortem morphometric data with the echocardiographic data (see below). We also expressed the diameter of the vessels in terms of the

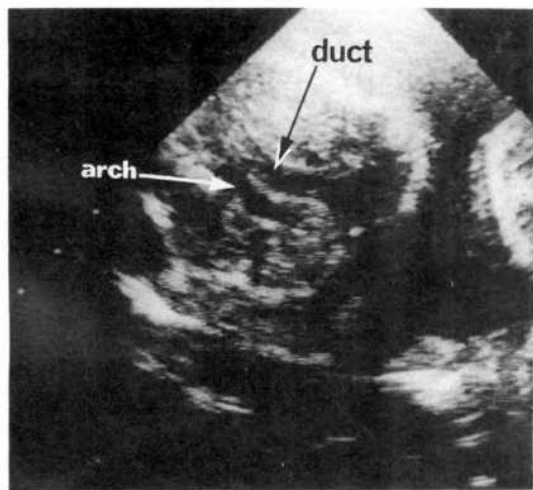


Fig 4 Echocardiogram (oblique horizontal view of the upper thorax showing the arch and duct in same section) taken obliquely across the thoracic inlet showing how, whenever possible, the arterial duct and the isthmus of the aortic arch were viewed in the same place.

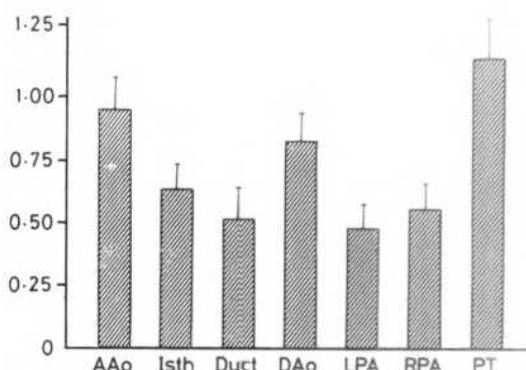


Fig 5 Histogram showing the mean (SD) of the ratio between the diameter of each vessel and that of the ascending aorta as determined from the postmortem data. AAo, ascending aorta before the origin of the brachiocephalic arteries; Isth, isthmus; duct, arterial duct; DAo, descending aorta; LPA, left pulmonary artery; RPA, right pulmonary artery; PT, pulmonary trunk.

descending aorta. We checked the validity of the flow-dependence rule,¹¹ which states that the sum of the squared diameters of the arterial branches is equal to the square of the diameter of the arterial stem itself. We expressed the results as squared diameters and calculated their linear regression to establish the relation between the isthmus, the arterial duct, and the descending aorta and also that of the pulmonary trunk and its branches.

ECHOCARDIOGRAPHIC STUDY

We studied the fetuses of 20 women attending our department for diagnostic fetal echocardiography who were studied between 23 and 27 weeks' gestation. They were selected on the basis of the image quality of the echocardiographic study. All fetuses were healthy at delivery and subsequently.

We used the Hewlett Packard 77020 AC and a 5 MHz medium focused probe for echocardiography. This system has an axial resolution of 0.9 mm and a lateral resolution of 1.4 mm. All patients had good quality images with the regions of the arch, duct, and isthmus being clearly visualised in several projections (figs 2 and 3). Only the dimensions of the descending aorta changed during the cardiac cycle. In the remainder of the arch and in the duct and pulmonary arteries the calibre of the vessels was more or less constant during systole and diastole. The ascending aorta was similarly of constant diameter and it, therefore, was chosen for purposes of comparison. All fetuses had a structurally normal heart as proven during fetal echocardiography and at postnatal follow up. The table shows the distribution

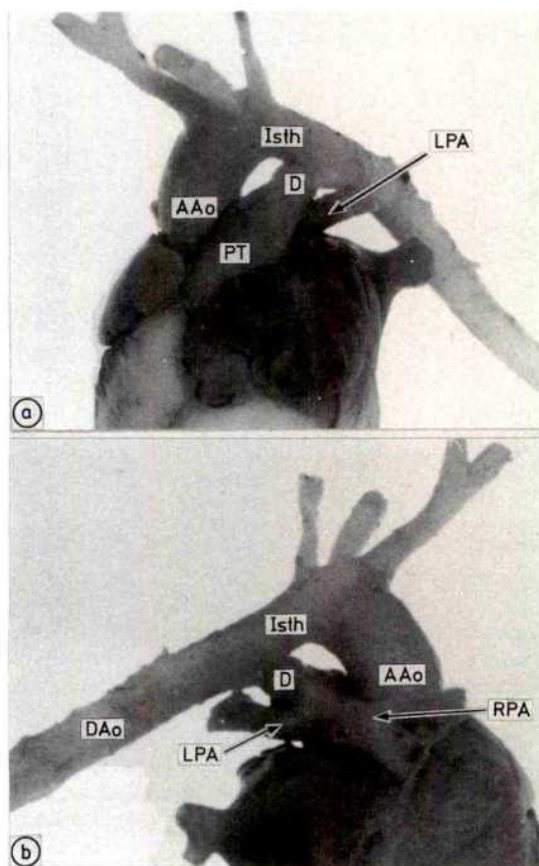


Fig 6 Heart and arch structures of a fetus of 20 weeks' gestation showing the size of the vessels. Note the absence of narrowing at the site of the isthmus. (a) Left anterior view and (b) right posterior view. See fig 5 for abbreviations.

of gestational age. The diameters of the ascending aorta and pulmonary trunk were measured at the level of the arterial valves, keeping the ultrasound beam perpendicular to the vessel walls wherever possible. The isthmus was measured as the smallest aortic diameter occurring immediately after the origin of the subclavian artery (fig 2). The right pulmonary artery and duct were measured at their origins (fig 3). Wherever possible we measured the duct and isthmus in the same projection and on the same stop frame (fig 4). We measured each vessel several times. Initially, five separate frames were measured and the results were averaged; these showed little deviation. Subsequently, therefore, three measurements of separate frames were taken at each level. The left pulmonary artery was not consistently imaged and, hence, was not included in the echocardiographic measurements. All measurements were taken by the same observer (LDA).

Results

POSTMORTEM DATA

In three specimens there was no discernible increase or decrease in the measured diameters of the vessels before and after fixation. The mean ratio between the isthmus and the ascending aorta was 0.63 (0.11) while that between the arterial duct and the ascending aorta was 0.51 (0.13) (fig 5; $p > 0.001$ by Student's *t* test). The ratios between the left and right pulmonary arteries and the ascending aorta were 0.48 (0.10) and 0.56 (0.10) respectively (fig 5). The isthmus was larger than the duct in 20 of the 30 cases (fig 6). It was smaller in seven of the 30 and the same in three specimens. The right pulmonary artery was larger than the duct in 16, equal to the duct in six, and smaller in eight of the 30. The left pulmonary artery was always smaller than the right pulmonary artery but was larger than the arterial duct in eight of the 30 specimens. The pulmonary trunk was larger than the ascending aorta in 24, of equal size in five, and smaller in only one of the 30 specimens. The ascending aorta was larger than the descending aorta in 24, equal in four, and smaller in two. Figure 7 shows the percentage difference between the diameter of each vessel and that of the descending aorta. The diameters of the pulmonary trunk and the ascending aorta were 46.07% and 24.77% more than that of the descend-

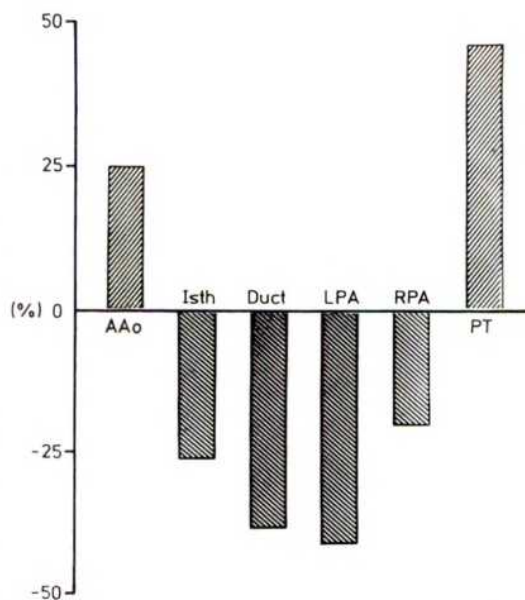


Fig 7 Histogram showing the percentage difference between the diameters of each vessel and that of the descending aorta as assessed from the postmortem data. See fig 5 for abbreviations.

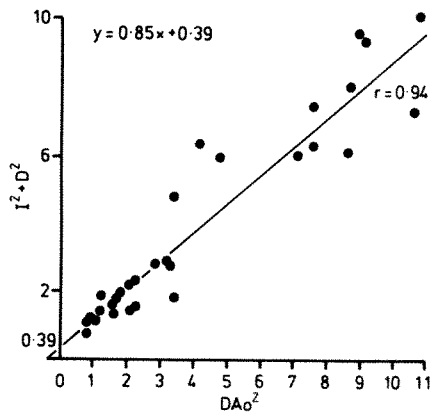


Fig 8 Regression line for the diameters of the descending aorta versus those of the arterial duct and isthmus expressed as squared diameters.

ing aorta. The diameter of the duct was 38.26% smaller than the descending aorta and the isthmus was 24.57% smaller. Figures 8 and 9 show the calculations for verification of the flow-dependence rule. The regression coefficients for the relations between the descending aorta versus its branches ($r = 0.94$) and the pulmonary trunk versus its branches ($r = 0.89$) both showed a good correlation.

ECHOCARDIOGRAPHIC DATA

The ratio between the isthmus and the ascending aorta was 0.73 (0.07) while that between the arterial duct and the ascending aorta was 0.7 (0.08). These differences are not statistically significant. The ratio between the right pulmonary artery and the ascending aorta (0.62 (0.06)) was similar to that of the duct (fig 10). The isthmus was found to be of larger diameter than the duct in 15 cases, of equal size in three, and smaller in only two cases. The right pulmonary artery was slightly smaller than the duct

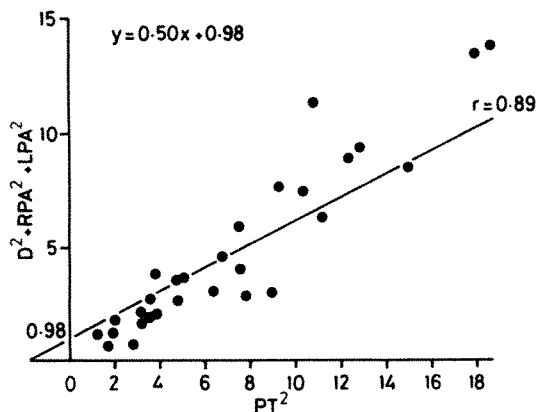


Fig 9 Regression line for the diameters of the pulmonary trunk versus those of the duct, and left and right pulmonary arteries expressed as squared diameters.

in all but one case. The pulmonary trunk was larger than the aorta in all cases.

Discussion

The first morphometric data on the size of the human isthmus and arterial duct were based on angiographic and postmortem data.^{1,2} These studies were obtained in postnatal, premature, and full term neonates. These are the only detailed morphometric studies of the pathways of the human fetal circulation. Current concepts of human fetal circulation are derived from the work of Rudolph *et al* who measured flow in the fetal lamb. Despite acknowledging some drawbacks, this group postulated that these findings are applicable to the human fetus.¹⁰ Accordingly, it is held that the development of vessels is proportional to the amount of blood carried by them. Similar flow, therefore, should produce vessels of similar diameter. Yet recent reviews by Rudolph *et al*^{10,12} conclude that the ascending aorta, which carries 35–40% of combined ventricular output, is similar in diameter to the descending aorta, which is presumed to carry about 70% of the combined ventricular output. The size of the ascending aorta is also thought to be comparable with that of the arterial duct (which carries 55% of the combined ventricular output) while the isthmus (10–15% of the combined ventricular output) is said to have a cross sectional area that is half that of the descending aorta.

Recent developments in fetal echocardiography have now given us the opportunity of studying directly the dimensions of these vessels in the developing human fetus. Such measurements taken during fetal life are needed because fixation and agonal changes may have different effects on the calibre of elastic and muscular vessels¹³ and isolation of the specimen might also cause premature contraction of the arterial duct. The echocardi-

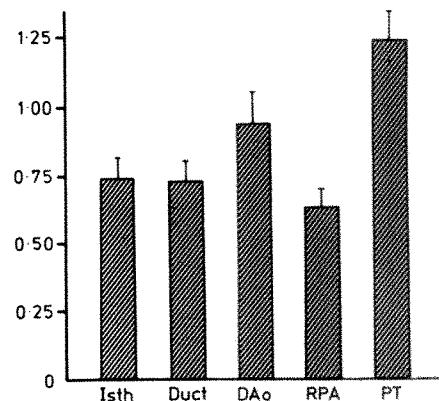


Fig 10 Histogram showing the mean (SD) of the ratio between the diameters of each vessel and that of the ascending aorta as calculated from the echocardiographic data. See fig 5 for abbreviations.

graphic technique too has drawbacks. To minimise error, we chose patients with the best quality images and where possible made measurements in the axial plane because it gives better resolution than the lateral plane. In particular, we took care to make measurements of the isthmus and arterial duct in the same projection. Taken overall, none the less, all these limitations can be overcome if the echocardiographic and postmortem measurements are compared. We found that although the absolute results of these studies differed, the ratios of vessel size obtained with the two techniques are similar. Taken together, they show that the isthmus and the arterial duct are usually similar in size and that occasionally the duct is smaller. The calibres of the isthmus and arterial duct measured echocardiographically were not significantly different. In contrast, morphological measurements showed that the isthmus was significantly larger than the arterial duct ($p < 0.001$). The discrepancy might be the result of greater shrinkage of the muscular duct relative to the elastic isthmus during fixation. But measurements in fresh specimens show no change in trend when compared with the same specimens after fixation. Similar findings have previously been reported.¹⁴

Our results, therefore, show that the isthmus is not as small during the middle period of fetal life as was generally assumed from data derived from animal models. Our observations support the "flow-dependence rule"¹¹—that the dimensions of main channels are proportional to the sums of the dimensions of their tributaries. We can make several propositions about the human fetus from our results. Our measurements show that the arterial duct has a smaller diameter at mid-gestation than previously thought. This suggests that flow through the human arterial duct may be less than previously assumed, or that the influence of flow on the size of the vessel is less. Alternatively, if the cardiac output from the right ventricle is as expected from animal models, then a greater amount of flow may go through the lungs. A further possibility is that the cardiac output from the right ventricle may be less, with flow to the pulmonary arteries being as previously thought.

Whatever the reasons, the aortic isthmus in the human fetus is larger and the arterial duct smaller than previously assumed. This suggests that the distribution of the circulation and the fetal flow patterns may be significantly different in the human fetus and the lamb fetus. In addition, it may be that the proportion of the cardiac output carried through the vessel may have a somewhat lesser effect on its size than previously thought. None the less, our study was performed on fetuses that were generally between the tenth and thirtieth weeks of gestation. Just as we have shown the dangers of extrapolating from animal models to the human, we caution against presuming that our conclusions can be applied to the

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later period of intrauterine life. Further studies are in progress to chart the dimensions of the arch vessels during this crucial period.

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The determination of atrial arrangement by examination of appendage morphology in 1842 heart specimens

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SUMMARY The morphology of the atrial appendages was examined in 1842 specimen hearts from patients with congenital lesions. The external and internal features that permitted the identification of the right and left appendages were studied in detail in one tenth of the hearts. These results were compared with a similar analysis of 25 normal hearts. This study showed that criteria for identification of right and left appendages were reliable. Application of these criteria to the overall collection identified the usual arrangement in 1776 (97%) hearts, a mirror image arrangement in eight (0.4%); left atrial isomerism in 22 (1.2%); and right atrial isomerism in 36 (1.9%). Fourteen (0.81%) had juxtaposed atrial appendages (13 with usual arrangement and one with left isomerism). This did not interfere with identification of the left and right atria on the basis of appendage morphology. In only two cases did the determination by atrial morphology produce a result that was inconsistent with the arrangement of the other thoracoabdominal organs. Further examination of the atria in these showed a mistake had been made in the initial assessment. The atrial arrangement can be accurately determined by the morphology of the atrial appendages.

The identification of the atrial arrangement is the first step in the analysis and diagnosis of complex congenital heart disease.^{1,2} Hitherto, the analysis of the syndromes of "visceral heterotaxy" has largely been based on identification of extracardiac associated lesions.³⁻⁶ Most commonly the presence of multiple spleens or absence of the spleen was used to determine and name syndromes which, in terms of thoracic arrangement, were known to be characterised by isomerism. There are many exceptions to the recognition of the atrial arrangement from the state of the spleen.^{7,8} The correlation between the bronchial and atrial arrangements is better⁷ but there are exceptions to broncho-atrial concordance.⁸ All indicates that an examination of the appendages

themselves may be the best guide to atrial arrangement and an earlier double blind study of a few hearts suggested that this was a practical approach.⁷ We have studied the morphology of the atrial appendages in all the congenitally malformed hearts in the Cardiopathological Museum collection at Children's Hospital of Pittsburgh.

Patients and methods

We examined all the hearts from the cardiopathological collection of Children's Hospital of Pittsburgh (a total of 1847 specimens). Two observers (SS and WD) independently examined the morphology of the atrial appendages in all the hearts. The external appearance of the appendage and the nature of its junction with the venous portion of the atrium were used to identify morphological leftness and rightness. The specific features that distinguished between the right and left atria were studied in more detail in every tenth heart of the collection. We compared the findings from this title of the collection with examination of 25 normal hearts.

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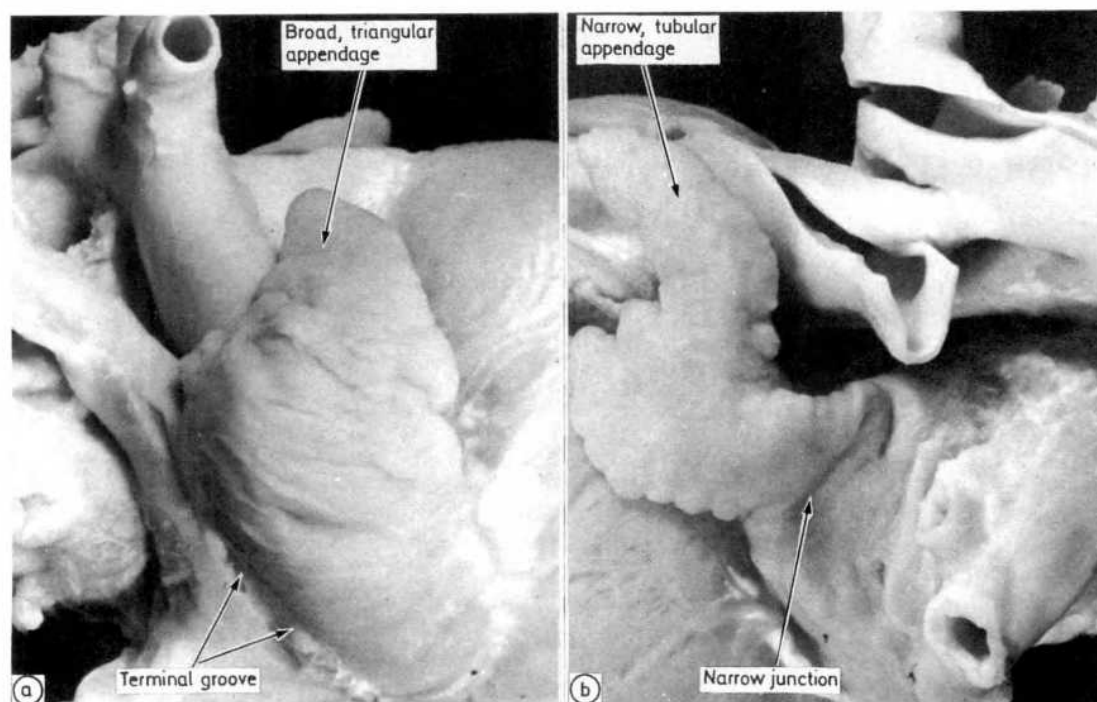


Fig 1 Typical external appearance of the atrial appendages. The morphologically right appendage (a) is broad and triangular with a wide junction with the venous component of the atrium. In contrast, the morphologically left appendage (b) is tubular, wavy, and has a narrow junction with the venous component.

Results

We excluded five hearts with severely damaged atrial appendages from the study. The morphologically right appendage in the remainder was characterised externally by its triangular shape together with its broad base and a hooked apex that in most cases pointed upwards (fig 1a). These features proved reliable differentiators in almost all of the hearts studied in detail (table). In a small number of cases, the external appearance of the right appendage was equivocal. In these we studied the internal morphology to confirm that this was the right appendage. The internal architecture was characterised by a broad junction between the systemic venous atrium and the appendage. There was a prominent crest (the "crista terminalis") at this junction. This was the most reliable distinguishing feature (table). The pectinate muscles were arranged at right angles to the crest and "spilled" out of the appendage posteriorly, continuing all around the atrioventricular junction to the post-eustachian sinus (fig 2a). The left appendage was tubular with a hooked apex that in most cases pointed downwards (fig 1b, table). The base of the appendage was narrow. Internal examination in doubtful cases showed that the junction of pulmonary venous atrium with the appendage was corre-

Table Results of detailed examination of the right and left atrial appendages in 25 normal hearts and one tenth of the collection of malformed hearts

Morphological feature	Normal hearts (25)		Malformed hearts (190)	
	Right	Left	Right	Left
Shape:				
Triangular	25	—	190	—
Tubular	—	25	—	178
Hypoplastic	—	—	—	8
Virtually absent	—	—	—	4
Direction of hook:				
Up	24	6	181	54
Down	1	19	2	116
Horizontal	—	—	7	14
Lacking	—	—	—	6
Terminal crest:				
Present	25	—	190	—
Absent	—	25	—	190
Junction with venous atrium:				
Broad	25	—	188	—
Narrow	—	25	1	187
Constricted	—	—	1	1
Absent	—	—	—	2
Spillage of pectinate muscles:				
Extreme	18	—	150	—
Pronounced	7	—	28	—
Moderate	—	—	12	—
Minimal	—	7	—	29
Nil	—	18	—	161

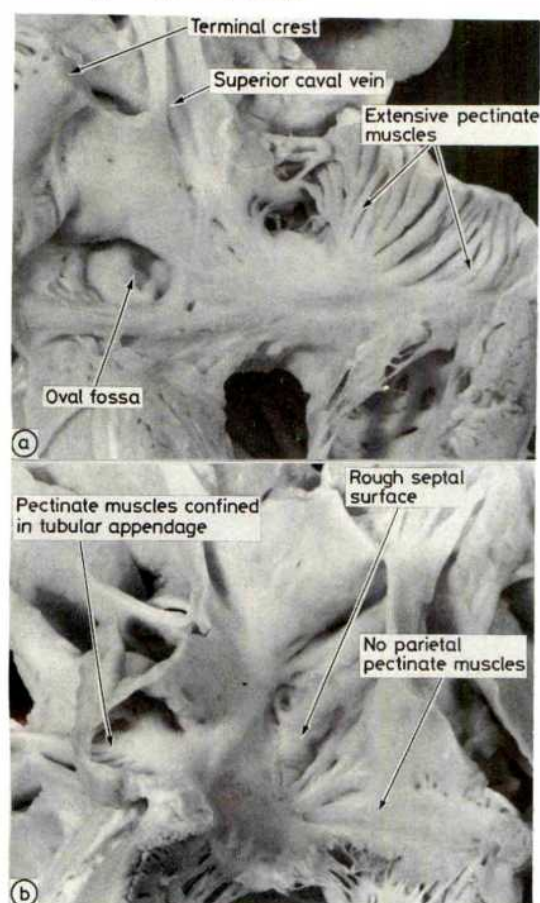


Fig 2 The internal morphology confirms the differences between the atrial appendages. The broad junction in the morphologically right appendage (a) is marked by the terminal crest (*crista terminalis*). The pectinate muscles extend all round the atrioventricular junction. In the morphologically left appendage (b), the pectinate muscles are confined within the appendage and there is no terminal crest.

spondingly narrow. Unlike the right junction there was no crest and tapered pectinate muscles "spilled" on to the atrial septum. The extension of the pectinate muscles round the parietal part of the left atrioventricular junction was confined within the appendage (fig 2b).

When we used these criteria to identify the appendages in the entire collection, we found that 1776 (97%) of the 1842 hearts had the usual atrial arrangement (*situs solitus*). Fourteen of these had juxtaposed atrial appendages, to the left in 12 and to the right in two (fig 3). The presence of juxtaposition did not affect the identification of atrial arrangement. Eight (0.4%) had mirror image atrial arrangement

(*situs inversus*, fig 4). Twenty two (1.2%) hearts had left atrial isomerism. The appendages were juxtaposed to the right of the arterial pedicle in one of these hearts but both appendages were clearly of left morphology (fig 3b). Thirty six (1.9%) hearts had right atrial isomerism (fig 5). None of these had juxtaposition of the atria. Two hearts were initially diagnosed incorrectly as showing right isomerism. Study of the necropsy records of these cases showed none of the expected thoracoabdominal stigmata of isomerism. Furthermore, the atrial septum was intact in each case. Re-examination showed that the original incision had produced the spurious impression of a broad junction between the appendage and the venous component of the left atrium. The pulmonary veins were normally connected in each case. It was clear that both hearts had usual arrangement of the atria.

Discussion

Precise determination of atrial arrangement is the basis for sequential segmental analysis of congenital heart disease.^{1,2} If the atrial arrangement is not known, then the atrioventricular junction cannot be analysed with certainty. As yet, there is no consensus on how best to identify atrial arrangement. To our knowledge all hearts have two atria that are either of right or left morphology. Determination of arrangement of these atria therefore stands or falls on the distinction between leftness and rightness. To make this distinction, as with any cardiac structure, we followed the principle originally introduced by Lev⁹ and subsequently dubbed the "morphological method" by Van Praagh and his associates.¹⁰ This principle states that structures should be identified according to the component part that is most universally present. For the ventricles, the morphology of the apical trabecular component must be used to determine rightness or leftness, since the ventricular inlets and outlets can be variously absent in malformed hearts. Application of this principle to the atrial chambers shows that the appendages must be the arbiters of leftness or rightness because the great veins can themselves be anomalously connected. The atrial septum can be absent without disturbing the basic anatomy of the atrial chambers. Detailed analysis of the appendages in one tenth of the hearts of the Pittsburgh collection, however, identified the most reliable morphological differences between left and right atria. Application of these criteria to the entire collection proved that it was possible to distinguish correctly between morphologically right and left appendages.

Our study confirms the earlier investigation of Macartney *et al.*⁷ This demonstrated that the shape of

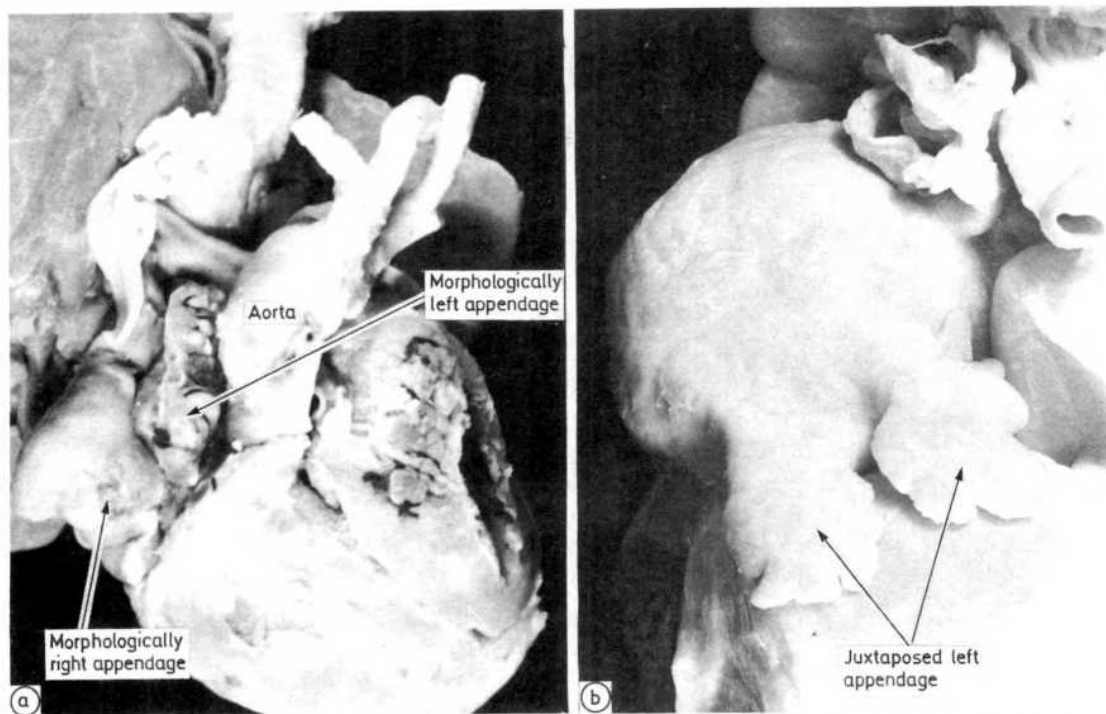


Fig 3 Two of the hearts had right sided juxtaposition of the atrial appendages. The shape of the appendages showed the usual arrangement (a) in one and left isomerism (b) in the other.

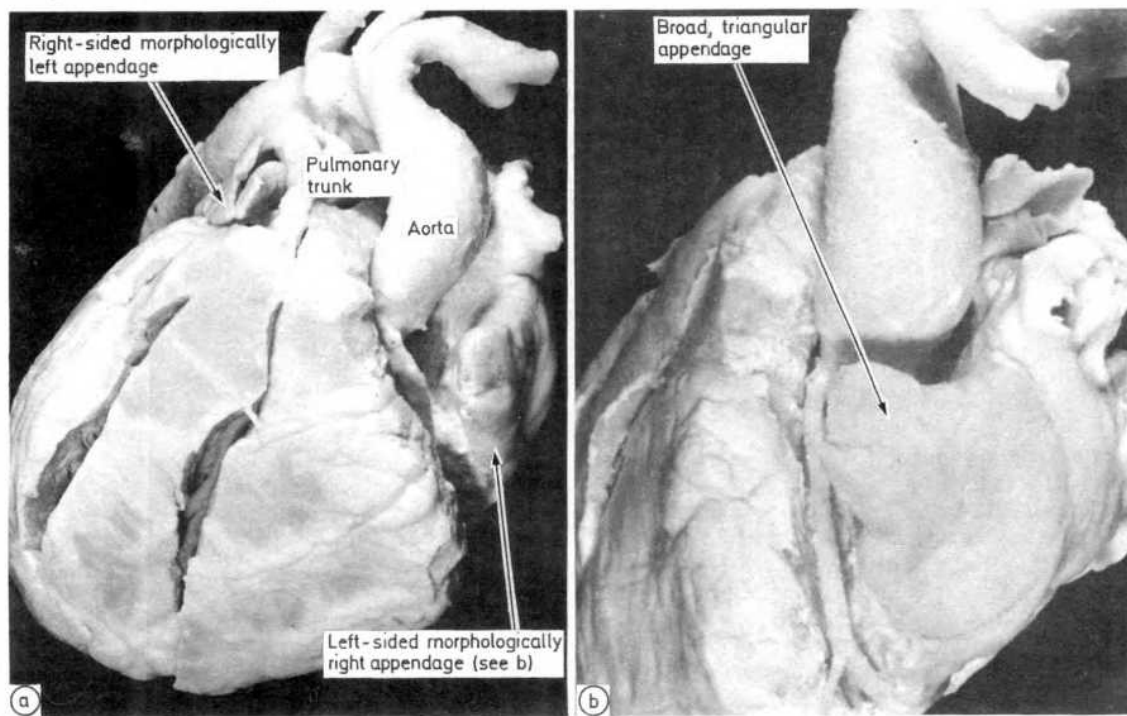


Fig 4 Eight hearts showed mirror image arrangement of the appendages. The heart shown was morphologically normal apart from the mirror imagery. It was in the right chest with its apex pointing to the right (a). The left sided appendage (b) was unequivocally of right morphology and the right sided appendage was of left morphology.

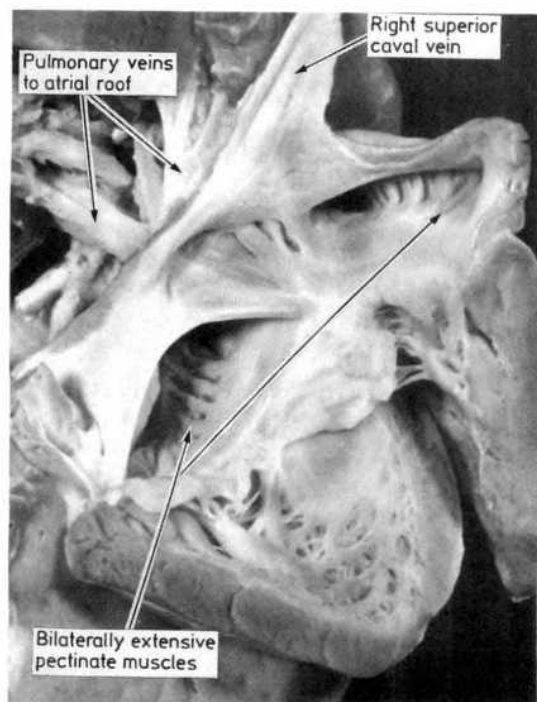


Fig 5 Thirty six hearts were readily diagnosed as having right atrial isomerism. The pectinate muscles extending all round both sides of the atrioventricular junction are obvious in this heart. It has a common valve connecting both atria to a dominant left ventricle.

the appendage was a simple and accurate guide to the identification of atrial arrangement. Our subsequent examination of the necropsy records of our cases with atrial isomerism endorses the conclusions of Macartney *et al.*,⁷ namely that categorisation according to atrial morphology is a much better guide to the so-called "splenic syndromes" than is the state of the spleen. In the study of Macartney *et al.*,⁷ 18% of the cases would have been incorrectly described on the rule based on the arrangement of splenic tissue. In our study, five cases with right isomerism (no spleen expected) had splenic tissue in their abdominal cavities. Three cases of left isomerism, in which multiple spleens would be expected, had solitary spleens while two more cases had double spleens. Taken together, this gives an incorrect diagnosis in 15% of our cases.

Our study shows that examination of the atrial appendages is by far the most accurate means of distinguishing the categories of atrial arrangement. The accuracy of the identified morphological markers for clinical diagnosis can only be assessed in a prospective trial.

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Balloon dilatation of the pulmonary valve in the first year of life in patients with tetralogy of Fallot: a preliminary study

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SUMMARY Fifteen infants with tetralogy of Fallot, who would otherwise have required a palliative operation, underwent balloon dilatation of the right ventricular outflow tract. The mean period of palliation was 8.5 months (range 0-26 months). The procedure was performed without serious complications on 88% of occasions.

This preliminary study suggests that balloon dilatation may be useful in the management of tetralogy of Fallot.

Some centres believe that the optimum time for correction of tetralogy of Fallot is after two years of age. The need for a palliative operation before this is determined by the severity of cyanosis and the frequency of cyanotic spells, both of which are related to the degree of right ventricular outflow tract obstruction. Palliative operation, however, has an appreciable mortality. The systemic to pulmonary artery shunts may require revision because of shunt failure and this may increase the risks of the subsequent definitive operation.

Balloon dilatation is an established treatment for pulmonary valve stenosis. We have used this technique in the management of an unselected group of infants with tetralogy of Fallot who would otherwise have required a palliative operation.

Patients and methods

Between December 1983 and December 1986, 15 infants (nine boys and six girls) had 24 balloon dilatations of the pulmonary valve for tetralogy of Fallot. Five children required more than one balloon procedure—two children had two, two children had three, and one child had four balloon dilatations on separate occasions. Their mean age at the first procedure was 3.3 months (range 0.5-9 months).

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Tetralogy of Fallot was an isolated finding in nine children. Two children had an associated persistent arterial duct, two had a secundum atrial septal defect, one an atrioventricular septal defect, and one had an aorto-pulmonary collateral artery as the sole blood supply to the left pulmonary artery.

On 19 occasions balloon dilatation of the pulmonary valve was performed because the patients were becoming increasingly cyanosed and on five occasions it was performed because of frequent cyanotic spells. In our hospital, all patients with tetralogy of Fallot who were being considered for palliative treatment underwent balloon dilatation as the procedure of choice rather than a shunt. Early in the series, the pulmonary valve could not be crossed at cardiac catheterisation in five patients. Treatment with a β blocker (propranolol) was continued in patients already on this treatment but was not started for the first time at the time of balloon dilatation.

Cardiac catheterisation and angiocardiology were carried out under general anaesthesia in all cases. The mean systemic arterial oxygen saturation was 75% (range 46-97%) and the mean pulmonary artery oxygen saturation was 64% (range 46-80%). The mean right ventricular outflow tract gradient, measured on 15 occasions, was 70 mm Hg (range 56-83 mm Hg).

We used balloons with external diameters of 6-15 mm for dilatation. The size of the balloon was selected on the basis of the size of the pulmonary valve annulus measured from the lateral projection of the right ventricular angiogram. Early in the series, dilatation was performed with balloons that we later recognised were too small. In the later cases we used

balloons with diameters that were approximately 33–40% larger than the pulmonary annulus. An exchange guide wire was passed through a 5 French Cournand or Multipurpose catheter and the tip was positioned in the distal right pulmonary artery. The balloon catheter was advanced over the guide wire until the midpoint of the balloon lay at the valve annulus. The balloon was inflated with dilute contrast to a pressure of 3–4 atmospheres and deflated immediately. For each dilatation procedure the balloon was inflated between two and four times. When we used larger balloons a constriction persisted at the site of the pulmonary valve annulus. The femoral artery pressure was monitored with a cannula whenever possible. The systemic and pulmonary oxygen saturations and right ventricular outflow tract gradient were measured at the end of the procedure.

Results

HAEMODYNAMIC FUNCTION

On 20 occasions the systemic arterial oxygen saturation increased by a mean of 18% (range 6–38%), on two occasions it remained the same, and on two occasions it deteriorated by 4% and 17%. Overall the systemic arterial oxygen saturation improved to a mean of 87% (range 65–98%; $p < 0.05$) after dilatation. The mean oxygen saturation in the pulmonary artery was 68% (range 52–89%) after dilatation and did not differ significantly from the value before dilatation. The mean residual systolic gradient across the right ventricular outflow tract was 64 mm Hg (range 45–83 mmHg). The gradient was increased in two patients by 10 mm Hg; however, the systemic artery saturation improved by 37% in one and by 12% in the other.

COMPLICATIONS

In all children there was a transient period of hypotension and bradycardia during balloon inflation, with spontaneous recovery within 30 seconds.

Table 1 Patients adequately palliated by balloon dilatation

	Case No						
	1	2	3	4	5	6	7
Age at presentation (mnth)	18	9	03	01	03	03	01
Age at first dilatation (mnth)	2	9	05	05	9	10	3
Age at follow-up (mnth)	20	18	4*	45	35	27	7
Period of palliation (mnth)	18	9	35	4	26	26	4

*Died.

Table 2 Patients who required systemic-pulmonary artery shunt after dilatation

	Case No			
	8	9	10	11
Age at presentation (mnth)	18	5	2	06
Age at first dilatation (mnth)	3	6	25	1
Age at shunt (mnth)	3	9	3	3
Period of palliation (mnth)	0	3	05	2

Two children required a short period of intermittent positive pressure ventilation after the procedure—one because of increasing cyanosis two hours after dilatation (11 days later a Waterston shunt was inserted) and the other because transient pulmonary oedema developed 18 hours after dilatation. In one patient group D streptococcal septicaemia developed after the procedure. This was treated with appropriate antibiotics. He died suddenly at home three months later, having been symptom free for three weeks; at necropsy vegetations were found on the tricuspid valve.

OUTCOME

Six children have not required further intervention during a mean follow up of 12.9 months (range 3.5–26 months). Four children have had a systemic to pulmonary artery shunt a mean of 1.6 months (range 0–3 months) after dilatation and four children have had a corrective operation six to 10 months (mean 8 months) after dilatation (tables 1–3).

OPERATIVE FINDINGS

The pulmonary artery and valve were inspected at the time of surgical correction. In two patients the valve was tricuspid without any evidence of tears affecting the cusps or commissures. The other two valves had tears; in one the valve was tricuspid and there was a split along the commissure between the posterior and the left cusps and in the second patient there was a tear of the posterior cusp itself. We saw no tears in the pulmonary arteries.

Table 3 Patients who had surgical correction after balloon dilatation of the pulmonary valve

	Case No			
	12	13	14	15
Age at presentation (mnth)	1	3	7	03
Age at first dilatation (mnth)	3	3	7	2
Age at correction (mnth)	13	12	13	9
Period of palliation (mnth)	10	9	6	7

Discussion

The mortality for total correction of tetralogy of Fallot is between 1% and 5%.¹ Although operation during infancy is associated with only a small increase in the frequency of early deaths, young age and small size remain important risk factors.¹ Many centres therefore recommend a staged approach with the creation of a systemic to pulmonary artery shunt before complete correction.²⁻⁴ This has the advantage of reducing the intensity of cyanosis and the frequency of cyanotic attacks. It also promotes the growth of the pulmonary valve annulus and the pulmonary arteries, which may reduce the need for insertion of transannular patches at the corrective operation and thus reduces the operative risks and achieves a better functional outcome.⁵⁻⁷

The creation of systemic to pulmonary artery shunts is, however, not without risk. The operative mortality of Blalock-Taussig and Waterston shunts varies between 0% and 13%.^{1,8-12} Approximately 10% of Blalock-Taussig shunts became occluded¹¹ and up to 16% of Waterston shunts produce kinking of the pulmonary arteries or pulmonary hypertension or both.¹²⁻¹⁴ Shunt failure may require either total correction before the optimum time or the formation of a second shunt; both procedures increase the risks of total correction.¹ In view of these problems there may be a place for an alternative form of palliation.

Balloon dilatation is now a recognised method of treatment for pulmonary valve stenosis and has recently been applied to pulmonary artery stenosis and hypoplasia.^{15,16} We have extended its use to infants with tetralogy of Fallot as an alternative form of palliation to systemic to pulmonary artery shunt operations. In this study adequate non-surgical palliation was achieved in 11 (73%) infants and four of them later had elective total correction. Dilatation is simple to perform and can be repeated if necessary. It requires an inpatient stay of only 48 hours compared with a stay of about seven days for a systemic to pulmonary artery shunt and does not need the resources of a cardiothoracic surgical centre. It also does not seem to increase the risks of subsequent corrective surgery.

Balloon dilatation for pulmonary valve stenosis, however, is not without risk. The potential immediate complications include the production of arrhythmias, haemorrhage, and femoral vein thrombosis.¹⁷ There are also reports of damage to the right ventricular outflow tract¹⁸ and the pulmonary valve,¹⁵ trunk,¹⁹ and branch arteries.¹⁶ Twenty one (88%) of our procedures were uncomplicated and of the four children who have undergone correction the only notable findings were splitting of the commissures. Previous balloon dilatation did not cause any

intraoperative complications.

We could not predict the subgroup of children who did not benefit from balloon dilatation. We are also uncertain of the effect of this procedure on the growth of the pulmonary annulus and artery. Patients with a predominantly valvar component to the right ventricular outflow tract obstruction may benefit most from this procedure.

This preliminary study suggests that balloon dilatation may be useful in the management of infants with severe tetralogy of Fallot and that it should be considered for the initial palliative treatment.

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Balloon dilatation of the aortic valve: limited success and early restenosis

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SUMMARY Balloon dilatation of the aortic valve was attempted 16 times in 15 patients with severe aortic stenosis. None died but one had a transient stroke after the procedure. At dilatation the gradient across the aortic valve was reduced by >30% in 69% of patients and the Gorlin valve area (calculated in 7/15 patients) increased by 30% in half. But a comparison of Doppler gradients measured before and one to two days after dilatation in 11 patients showed a >30% reduction in the simultaneously measured gradient in only four. Doppler gradient was the most accurate predictor of symptomatic benefit and a fall in Doppler gradient persisted mainly in patients whose peak to peak gradient fell by at least 40% at the time of the procedure.

Balloon dilatation of the aortic valve is a relatively safe procedure but it is less successful than previous reports suggest, perhaps because of early restenosis. Some forms of aortic stenosis may be more amenable to this procedure than others.

Since the original description by Cribier¹ of balloon dilatation of the aortic valve in adults with severe aortic stenosis several centres have adopted the technique. Although its success is not yet established early results suggest an improvement in symptoms in a high proportion of patients.²⁻⁶ Few data are available on longer term success although Cribier's group has reported a restenosis rate of 22% at a mean of 17 weeks after the dilatation. Our early results differ from those already published.

Patients and methods

Fifteen elderly patients (mean (SD) age 77 (5.5) years) with severe aortic stenosis were recommended for balloon dilatation of the aortic valve because they were not suitable for aortic valve replacement (table 1). In some patients operation was absolutely contra-indicated, while in others balloon dilatation was carried out because it had a lower risk than aortic valve replacement. Table 2 shows details of the procedure. We used balloons with diameters of 12-25 mm. Some were single chamber (Mansfield Single Lumen) and some were triple lumen Trefoil (21 mm or 25 mm). Simultaneous aortic valve gradients were

Table 1 Patient details and reasons for balloon dilatation of the aortic valve

Patient	Age	Sex	Symptoms*	Reason for balloon dilatation
1	79	F	D IV, A IV	Frail
2	85	F	D IV	Frail
3	71	M	S, A II	Frail
4	73	M	A II, D II	Disseminated carcinoma
5	89	M	D IV	Age
6	82	F	A IV, D III	Frail
7	68	F	D IV	Frail
8	76	M	D IV, A II	Pulmonary disease
9	77	F	D IV, A II	Frail
10	81	M	D IV	Carcinoma
11	75	F	D IV, A III, S	Frail
12	76	F	S	Carcinoma
13	76	F	D IV	Stroke
14	72	M	D IV, A III	Pulmonary disease
15	79	F	D IV	Frail, diabetes

*D, dyspnoea, A, angina; S, syncope; I-IV, New York Heart Association grades of exertion necessary to produce symptoms

recorded either with a second catheter in the aorta or by comparison with femoral arterial pressure after measurement of downstream augmentation. We measured cardiac output by thermodilution in seven patients before and after dilatation and calculated the area of the aortic valve by the Gorlin formula⁸ using pressure recordings taken within one minute of the

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Table 2 Details of procedure

Patient	Approach	CAD*	Balloon type	Balloon size (cm)
1	Femoral	0	Triple lumen	2.1
2	Femoral	?	Single lumen	1.2
3	Brachial	0	Single lumen	2.0
4	Brachial	0	Triple lumen	2.1
5	Femoral	3VD	Single lumen	1.5*
6	Femoral	0	Single lumen	1.2*
7	Femoral	0	Single lumen	2.0
8a	Brachial	0	Single lumen	1.2
8b	Femoral	?	Single lumen	1.2*
9	Femoral	?	Triple lumen	2.1
10	Femoral	?	Single lumen	2.0
11	Femoral	?	Single lumen	2.0
12	Femoral	?	Triple lumen	2.1
13	Femoral	0	Triple lumen	2.1, 2.5
14	Brachial	0	Single lumen	2.0
15	Femoral	2VD	Single lumen	2.5

*Two balloon technique.

CAD, coronary artery disease; VD, vessel disease

cardiac output measurement. The aortic valve gradient was also estimated by Doppler echocardiography one to two days before and again one to two days after the procedure. We crossed the aortic valve with a guide wire and advanced the balloon catheter across the aortic valve. For the first patients we used a manometer to monitor the inflation of the balloon to 6 atm, but later we assessed full inflation by visual appearance. If the positioning of the balloon was unstable it was inflated slowly initially and then rapidly fully expanded in an attempt to lock it in place. In one patient the balloon was inflated in the left ventricle and pulled back into the aorta. Inflation was maintained for 15–30 seconds. Patient 8

underwent two separate procedures, so there were 16 procedures in 15 patients.

Results

The mean (SD) peak to peak pressure drop across the aortic valve before the procedure was 86 (29) mm Hg (table 3). Immediately after the procedure the mean gradient had fallen to 59 (29) mm Hg. Eleven procedures were attended by a fall in the aortic valve gradient of > 30% and five out of seven patients showed a rise in Gorlin valve area. We measured gradients by Doppler echocardiography before and after 13 procedures. Only four patients showed a decrease of > 30%. The mean value fell from 90 (27) mm Hg to 75 (28) mm Hg. In four patients there was an improvement in dyspnoea that persisted for at least one month. Two of these patients had Doppler gradients of 100 mm Hg both before and after balloon dilatation. One patient had symptomatic improvement for two days. One patient had no further syncope (her only symptom). Nine patients experienced no relief of symptoms.

There were several complications, mostly minor. In one patient pulmonary oedema developed during a first unsuccessful dilatation, and a small stroke developed that resolved completely after a second unsuccessful procedure. Systolic aortic pressure had fallen by ≥ 30 mm Hg in six patients at the end of the procedure. One patient required transfusion and another needed fluid replacement for symptomatic hypotension. In one patient a ruptured right external iliac artery was repaired.

Seven patients were referred for operation after one or two unsuccessful attempts at balloon dilata-

Table 3 Invasive and non-invasive assessment of aortic valve gradient before (pre) and after (post) dilatation. (s) = symptomatic benefit

Patient	Invasive assessment						Change in systolic BP (mm Hg)	Non-invasive assessment	
	Aortic valve gradient (mm Hg)		Cardiac output (l/min)		Aortic valve area (cm ²)			Doppler aortic valve gradient (mm Hg)	
	Pre	Post	Pre	Post	Pre	Post		Pre	Post
1	100	50	4.6	4.6	0.67	0.78	+ 10	90	80
2	80	55	2.3	2.1	0.33	0.29	- 50	70	70
3	115	80	—	—	—	—	0	90	90
4	70	40	3.8	4.7	0.61	0.83	+ 25	65	65
5 (s)	40	5	2.0	1.6	0.41	0.83	- 15	30	16
6	150	100	2.4	2.2	0.22	0.26	+ 10	—	—
7	100	100	3.1	3.31	0.40	0.61	- 110	125	135
8a	90	30	—	—	—	—	+ 5	80	70
8b	65	40	—	—	—	—	0	70	65
9 (s)	75	35	—	—	—	—	0	120	64
10 (s)	90	60	—	—	—	—	- 10	100	100
11 (s)	70	70	—	—	—	—	- 50	100	100
12 (s)	70	40	—	—	—	—	- 30	120	64
13	65	80	—	—	—	—	0	110	65
14	60	50	6.2	8.4	0.77	0.74	- 30	—	—
15	140	110	—	—	—	—	- 100	—	—

tion. Three had senile tricuspid aortic stenosis without commissural fusion. Three had bicuspid valves. At operation none of these valves showed any evidence of being disrupted by balloon dilatation. In the patient with a rheumatic valve there was partial release of the fused commissures after dilatation. Inspection of the heart distant from the valve showed damage to the left ventricle in three patients that was presumably caused by balloon dilatation. Two patients had bruising of the apex, and in one of them there was an apical thrombus. This patient had a stroke at the time of the second balloon dilatation, which suggested that the second procedure might have dislodged an apical thrombus formed after the first procedure. One patient had bruising over the territory of the left anterior descending coronary artery that was associated with a significant haemopericardium.

Subsequent operation was complicated by anterior myocardial infarction in the patient with apical thrombus (who had normal coronary arteries) and another patient had a major stroke and died.

Discussion

The incidence of aortic stenosis rises with age and although replacement is the best treatment some patients are not suitable for major surgery while in others the risk of the procedure is too high. For this reason the prospect of a low risk percutaneous procedure that can at least palliate the condition is attractive. Cribier's pioneering work and the early results from other laboratories suggest that the risks associated with balloon dilatation are low and that the procedure produces an immediate acceptable reduction of 40–50% in the pressure drops across the aortic valve. Furthermore, many patients have reported an improvement in symptoms that persisted for several months.^{2,6} So far there are few data on long term follow up.

Our results for the improvement measured at the time of the procedure resemble those of other groups. The aortic valve gradient was reduced by mean (SD) of 32 (26)%, and the area of the aortic valve increased in five of the seven patients for whom it could be calculated. But there were appreciable changes in cardiac output during the procedure that made the haemodynamic assessment less reliable. For example, one patient in whom the aortic valve gradient remained unchanged showed a significant increase in aortic valve area because cardiac output increased. This emphasises the importance of using area rather than gradient to assess the effects of dilatation. Assessment of aortic valve gradient by Doppler echocardiography may be more reliable because it is made in the basal state in a relaxed, pain-free, and

haemodynamically stable patient. Although pressure drops across the aortic valve measured by Doppler echocardiography do not always correlate with those measured at catheterisation intra-patient comparisons of Doppler measurements are likely to be more accurate. In the present study the results of assessment by Doppler echocardiography were disappointing, but they correlated well with symptomatic benefit in all but two patients, who had an improvement in symptoms despite there being no reduction in Doppler gradient.

We encountered similar difficulties as those of other groups. The most life threatening is perforation of the left ventricle by the guide wire. We attempted to form a large loop of guide wire in the left ventricle, and we found that a J-tipped exchange guide wire with a large diameter curve was best for this purpose. The use of longer balloons and rapid inflations may increase balloon stability, but larger balloons may be difficult to inflate and deflate rapidly. For this reason we no longer use manometers for inflation and are guided by the appearance of the balloon on the image intensifier. Stiffer catheters and guide wires increase the stability of the balloon position and pressure on the guide wire counteracts the tendency for the balloon to be pushed across the valve from its position in the left ventricle.

Seven patients proceeded to aortic valve replacement because their symptoms were not relieved by balloon dilatation. In only one patient was there any visual evidence that the preceding balloon dilatation had appreciably altered the valve. This was the only rheumatic valve in the series and the fused commissures were partially split. Valves with commissural fusion might be expected to respond to balloon dilatation, and if this were true rheumatic valves should be the easiest to dilate. Some bicuspid valves have a small amount of commissural fusion but the main mechanism of stenosis is increased rigidity and calcification of the valve cusps themselves. Senile tricuspid aortic stenosis is also caused by rigidity of cusps rather than by commissural fusion.

We know that the technique and equipment have improved since we treated this group of patients; even so a comparison of our early results and the early results of others who used similar techniques remains valid. The shortcomings of the technique may be reduced by developments in equipment and refinements in patient selection, but it is likely that a proportion of "suitable" patients will not respond to balloon dilatation despite advances in technique.

Balloon dilatation is already an important palliative clinical tool and will complement operation in the treatment of calcific aortic stenosis in certain groups of patients. If our results are confirmed by

others and balloon dilatation is less successful than previous reports suggest, it would be an advantage to be able to select patients with valves that are most likely to be successfully dilated. This depends on establishing the underlying aetiology of the aortic stenosis and on relating this to the success rates.

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Effects of increasing afterload on early diastolic dysfunction in hypertrophic non-obstructive cardiomyopathy

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SUMMARY The effects of increasing afterload on early diastolic dysfunction in 10 patients with hypertrophic non-obstructive cardiomyopathy were studied by computer assisted analyses of digitised M mode echocardiograms. Infusion of angiotensin II increased the end systolic pressure by a mean (SD) of 36.2 (10.3) mm Hg. As the afterload increased early diastolic dysfunction tended to become more normal: the interval and the change in dimension between minimal cavity dimension and mitral valve opening decreased and the duration of rapid diastolic filling and the accompanying change in dimension increased. None the less, the end diastolic dimension and thus the overall diastolic filling remained unchanged.

Impaired early diastolic function in hypertrophic cardiomyopathy is at least partly caused by altered loading conditions.

In hypertrophic cardiomyopathy diastolic function is impaired especially in early diastole.¹⁻³ Dysfunction in early diastole is probably caused by prolonged or incomplete relaxation and reduced distensibility of the left ventricle.⁴⁻⁶ Recently, Brutsaert *et al* showed that relaxation was significantly dependent on loading conditions,^{7,8} which suggested that impaired relaxation in hypertrophic cardiomyopathy could be to some extent the result of reduced wall stress.⁸

We have used non-invasive techniques to analyse the effects of increasing afterload on early diastolic dysfunction in patients with hypertrophic non-obstructive cardiomyopathy without mitral regurgitation.

Patients and methods

PATIENTS

We studied 10 patients (aged 21-61) with hypertrophic non-obstructive cardiomyopathy. All of them had had diagnostic cardiac catheterisation. Patients with left ventricular outflow tract obstruction and mitral valve regurgitation were excluded. Table 1 shows the patient data. All medications were stopped

at least 12 hours before the examination. Six patients had been taking oral verapamil (240-320 mg) and four patients were not on medication.

CONTROLS

We also studied 30 healthy volunteers (aged 18 to 30). None had a history of cardiovascular disease. Physical examination, electrocardiography, M mode, and cross sectional echocardiography showed no abnormalities. None of them was taking medications.

ECHOCARDIOGRAMS

Echocardiograms were performed with a Hewlett Packard 77020A ultrasound imaging device with a 3 MHz transducer. M mode echocardiograms were recorded while the left ventricular short axis was continuously visualised by cross sectional echocardiography. We took care to record the M mode echocardiogram through the centre of the left ventricular short axis with the ultrasound beam perpendicular to the posterior wall. The M mode echocardiogram and cross sectional echocardiogram were recorded at the tip of the mitral valve leaflets in standard position with a paper speed of 100 mm/s.⁹ The transducer was held in position for all measurements and all echocardiograms were recorded by one echocardiographer. Intraobserver and interobserver variability was below 7% for all measurements. A carotid pulse tracing was recorded

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Table 1 Patient data and baseline values

Case	Age (yr)	Sex	D_{ed} (cm)	PW_{ed} (cm)	SW_{ed} (cm)	Verapamil (oral)
1	47	M	3.75	1.2	2.7	320 mg
2	50	M	4.1	1.6	2.8	240 mg
3	56	M	5.2	1.3	3.2	—
4	42	M	4.9	1.5	2.5	—
5	41	M	5.0	1.2	3.1	—
6	53	F	5.1	1.2	1.6	—
7	61	F	4.3	1.2	2.2	240 mg
8	36	M	4.0	1.3	2.7	—
9	38	M	3.65	1.5	2.9	240 mg
10	21	F	3.3	3.0	3.1	240 mg

D_{ed} , end diastolic left ventricular dimension; PW_{ed} , end diastolic posterior wall thickness; SW_{ed} , end diastolic septal wall thickness

simultaneously with the M mode echocardiogram. This was corrected for pulse transmission delay by aligning it with the aortic valve echocardiogram.

MEASUREMENT OF END SYSTOLIC PRESSURE

Systolic and diastolic blood pressures were measured by a Dinamap 845 Vital Signs Monitor (Criticon Inc). This device estimates central aortic pressure accurately over a wide range of pressures, independently of cardiac index, systemic vascular resistance, heart rate, and body surface area.¹⁰ The end systolic pressure was estimated by the method of Stefadourous *et al*¹¹ by linear interpolation of the height of the dicrotic notch of the indirect carotid pulse tracing.^{10,11}

STUDY PROTOCOL

All examinations were performed with the patient at rest and semi-supine. The patients relaxed for at least 15 min before the examination. Intravenous atropine (0.01 mg/kg) was given before the examination to reduce reflex cardiac slowing caused by baroreceptor stimulation.¹²⁻¹⁴ After baseline recordings the blood pressure was slowly increased by the infusion of angiotensin II (0.5–3.5 µg/min). We attempted to increase the systolic blood pressure to 30 mm Hg above baseline values. We obtained simultaneous recordings of the M mode echocardiogram, carotid pulse tracing, and arterial blood pressure when pressure was highest. We also recorded the cross sectional echocardiogram on a video tape recorder.

Informed consent was obtained from all patients and the study protocol was approved by the local committee for human research.

COMPUTER ASSISTED ANALYSES

We accepted only high quality echocardiograms for analysis. The M mode echocardiograms were digitised with a Cardio 200 computer (Kontron Image Analysis). Three consecutive cardiac cycles were analysed and the mean was used for further calculations. We made the following time and dimensional measurements.

MEASUREMENT OF TIME INTERVALS

We used the start of the Q wave of the electrocardiogram as the zero reference point. The interval between the point where the fibre shortening velocity curve crossed zero and mitral leaflet separation was regarded as the interval between minimum cavity dimension and opening of the mitral valve (fig 1).¹⁵⁻¹⁷

MEASUREMENT OF DIMENSIONS AND DIMENSIONAL CHANGES

The end diastolic left ventricular dimension (DD) was measured at the start of the first Q wave of the cardiac cycle being analysed. The left ventricular dimension at aortic valve closure was taken as the end systolic dimension (DS). Fractional shortening (FS) was calculated as a parameter of systolic ejection:

$$FS = \frac{(DD - DS)}{DD} \times 100\%$$

The maximal rate of fibre lengthening was measured as the maximum of the first derivative of the instantaneous left ventricular internal dimension curve¹⁵ (fig 1).

The change of dimension between minimal cavity dimension and mitral valve opening was defined as^{16,17}

$$dDS - MO = \frac{DMO - DS}{DD2 - DS} \times 100\%$$

where DS is the minimal cavity dimension; DMO the dimension at mitral valve opening; and DD2, the end diastolic dimension at the end of the cardiac cycle.

The end of rapid diastolic filling was defined as the point at which the velocity of fibre shortening had decreased to 50% of its peak value³ (fig 1). The change of dimension with rapid diastolic filling (dRF) was calculated as:

$$dRF = \frac{DRF - DMO}{DD2 - DMO} \times 100\%$$

where DRF is the dimension at the end of rapid diastolic filling; DMO, the dimension at mitral valve opening; and DD2, the end diastolic dimension at the end of the cardiac cycle.

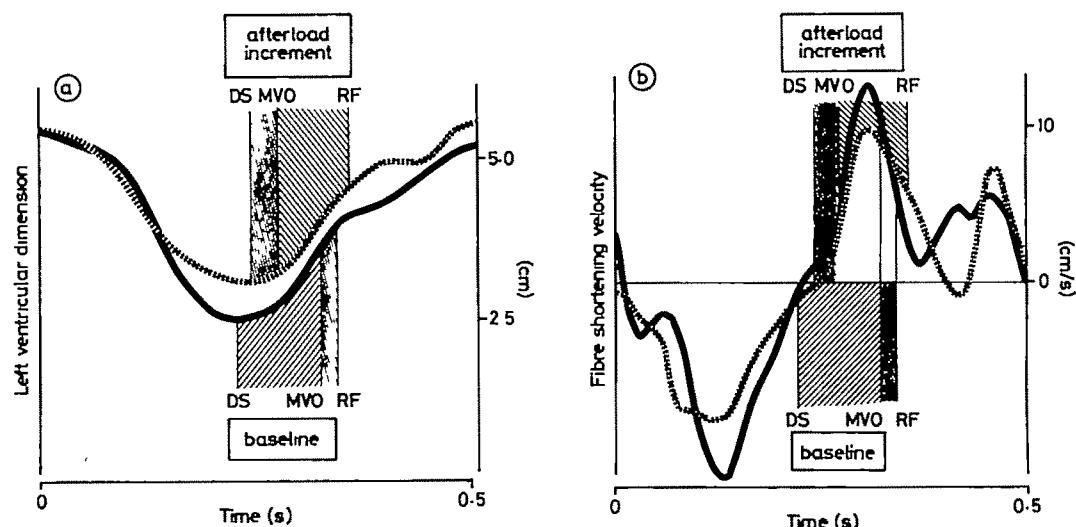


Fig 1 (a) Change in instantaneous left ventricular dimension and its first derivative (b) at baseline conditions (black line) and with increased afterload (broken line). When the afterload was increased early diastolic filling tended to become more normal—the interval and change of dimension between minimal cavity dimension (DF) and mitral valve opening (MVO) decreased and the duration and change of dimension with rapid diastolic filling (RF) increased. End diastolic dimension remained unchanged, while minimum cavity dimension and maximal fibre lengthening rate decreased.

Septal and posterior wall thickness were measured at end diastole as defined above.

STATISTICAL ANALYSIS

We used a paired *t* test to compare changes with increasing afterload in individuals. A *p* value of less than 0.05 was regarded as statistically significant.

Results

END DIASTOLIC PRESSURE AND SYSTOLIC EJECTION

The average (SD) increase of the end systolic pres-

sure was 36.2 (10.3) mm Hg ($p < 0.0001$) and the baseline end systolic pressure was 107 (15.6) mm Hg (table 2, fig 2). This increase of the end systolic pressure was accompanied by an average reduction in fractional shortening of 13.2 (3.97)% (absolute change) ($p < 0.0001$); the baseline fractional shortening was 49.4 (9.2)% (fig 2, tables 2 and 3). The heart rate showed no significant change during the increase in afterload (table 2).

DIMENSIONAL CHANGES IN EARLY DIASTOLE

During baseline conditions the average change of dimension between the minimum dimension and

Table 2 Echocardiographic and pressure data at baseline conditions and after afterload increment

Case	Baseline conditions									
	HR (beats/min)	P_{es} (mm Hg)	D_{ed} (cm)	D_{es} (cm)	FS (%)	$tDS-MO$ (ms)	$dDS-MO$ (%)	tRF (ms)	dRF (%)	VLR_{max} (cm/s)
1	56	111	3.75	2.0	47	150	20	75	26	7.3
2	59	120	4.1	2.15	48	125	49	20	20	10.0
3	63	113	5.3	2.5	53	150	55	40	13	13.1
4	76	93	4.9	2.6	47	169	43	80	30	13.3
5	59	116	5.0	2.6	48	150	71	45	8	6.4
6	74	117	4.9	2.6	55	105	21	120	43	13.0
7	65	126	4.3	3.05	29	155	40	60	8	7.1
8	93	99	4.0	1.6	60	140	38	40	0	13.8
9	72	106	3.65	1.4	62	155	64	60	32	10.5
10	67	73	3.3	1.8	55	120	20	120	40	11.3

HR, heart rate; P_{es} , end systolic pressure; D_{ed} , end diastolic left ventricular dimension; D_{es} , end systolic left ventricular dimension; FS, fractional shortening; $tDS-MO$, time between minimal cavity dimension and mitral valve opening; $dDS-MO$, change of dimension between minimal cavity dimension and mitral valve opening; tRF , time of rapid filling; dRF , change of dimension with rapid diastolic filling; VLR_{max} , maximal fibre lengthening rate.

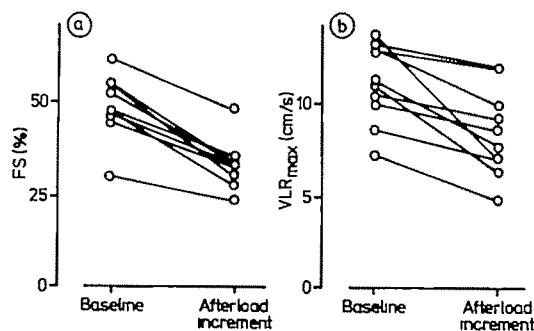


Fig 2 (a) Individual data for fractional shortening (FS) during baseline conditions and during increased afterload. Fractional shortening decreased by 13.2 (4.0)% (absolute change) during the increase in afterload, from a mean value of 49.4 (9.2)% at baseline ($p < 0.0001$). (b) Individual data for the maximum rate of fibre lengthening (VLR_{max}) at baseline conditions and during increased afterload. The maximum rate of fibre lengthening decreased by 25 (13.1)% when the afterload was increased ($p < 0.001$).

mitral valve opening was 42 (18.2)% and the change of dimension during rapid diastolic filling was 22 (14.6)% (table 2). At peak pressure the change in dimension between minimal dimension and mitral valve opening decreased by 26 (16.0)% (absolute change) ($p < 0.001$) (fig 3, tables 2 and 3) and the change of dimension with rapid diastolic filling was reduced by 19 (15.7)% (absolute change) ($p < 0.01$) (fig 3, tables 2 and 3). The maximal fibre lengthening rate showed a relative decrease of 25 (13.1)% from the baseline value ($p < 0.001$) (fig 3, tables 2 and 3).

END DIASTOLIC DIMENSION

The end diastolic left ventricular dimension showed no significant change when the afterload was increased (average increase 0.14 (0.22) cm; NS) (table 2).

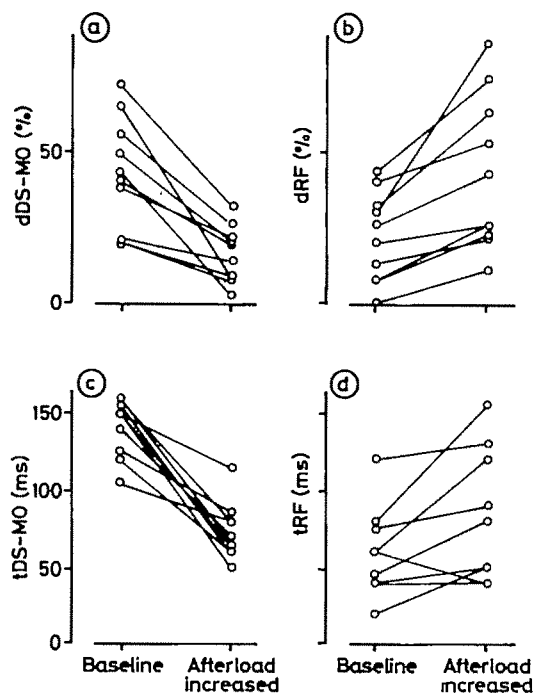


Fig 3 Individual data points for the variables of early diastolic function for baseline conditions and during increased afterload. The change of dimension between minimal cavity dimension and mitral valve opening (dDS-MO) tended to decrease to normal values with increasing afterload (a). The absolute change was 26 (16)% ($p < 0.001$). The change of dimension with rapid diastolic filling (dRF) (b) decreased by 19 (16)% (absolute change) ($p < 0.01$). The interval between minimal cavity dimension and mitral valve opening (tDS-MO) (c) panel decreased by 70 (28) ms ($p < 0.0001$) and the duration of rapid diastolic filling (tRF) (d) by 33 (25) ms ($p < 0.01$).

Increased afterload

HR (beats/min)	P _a (mm Hg)	D _{ed} (cm)	D _{es} (cm)	FS (%)	tDS-MO (ms)	dDS-MO (%)	tRF (ms)	dRF (%)	VLR _{max} (cm/s)
58	143	3.75	2.45	35	50	8	90	42	7.3
60	153	4.1	2.6	36	85	20	50	25	8.7
63	148	5.4	3.5	35	60	26	50	21	10.0
78	123	5.5	3.95	28	65	3	155	84	12.1
56	162	5.3	3.4	36	115	32	80	21	6.4
81	163	5.1	3.0	41	80	14	130	52	12.1
65	140	4.2	3.2	24	70	20	40	15	4.9
86	122	4.3	2.4	44	70	21	40	15	8.2
72	132	3.7	1.9	49	60	6	120	62	9.3
68	120	3.2	2.1	34	60	9	60	73	7.8

Table 3 Intraindividual changes during increased afterload in hypertrophic non-obstructive cardiomyopathy

Case	P_a (mm Hg)	FS (%)	VLR_{max} (cm/s)	$tDS-MO$ (ms)	$dDS-MO$ (%)	tRF (ms)	dRF (%)
1	32	-12	-16	-100	-12	15	16
2	33	-12	-13	-40	-29	30	5
3	35	-18	-24	-90	-29	10	8
4	50	-19	-9	-95	-40	75	54
5	46	-12	-42	-35	-39	35	13
6	46	-14	-7	-25	-7	10	9
7	24	-5	-30	-85	-20	30	7
8	23	-16	-41	-70	-17	0	11
9	26	-13	-12	-95	-58	60	30
10	47	-11	-31	-60	-11	60	33
Mean	36	-13	-25	-70	-26	33	19
SD	10.3	4.0	13.1	27.9	16.0	25.2	15.7
p	< 0.0001	< 0.0001	< 0.001	< 0.0001	< 0.001	< 0.01	< 0.01

All changes are given as absolute values except the change of the maximal fibre lengthening rate (VLR_{max}) which is given as percentage change of the baseline value.

See table 2 for abbreviations

CHANGES OF TIME INTERVALS IN EARLY DIASTOLE

The mean interval between minimal dimension and mitral valve opening was 141 (17) ms at baseline conditions and the duration of rapid diastolic filling was 66 (33.5) ms (table 2). At maximum pressure the time between minimal dimension and mitral valve opening decreased by 70 (28) ms ($p < 0.0001$) (fig 3, tables 2 and 3), and the time of rapid diastolic filling by 33 (25) ms ($p < 0.01$) (fig 3, tables 2 and 3).

Discussion

In severe hypertrophy the afterload has to be analysed in terms of wall stress.^{18,19} But in hypertrophic cardiomyopathy calculation of wall stress is difficult.²⁰ The myocardial fibre disarray, asymmetric hypertrophy, and irregular shape of the left ventricle (in particular at end systole) may lead to major errors if the current formulae for calculation of circumferential or meridional wall stress are used. This is because in all models for calculation of wall stress the shape of the left ventricle is assumed to be ellipsoid, a sphere, or a cylinder.²¹⁻²³ These simplifications do not reflect the altered shape of the left ventricle in hypertrophic cardiomyopathy, particularly at end systole, when deformation is greatest. Because of these difficulties we did not attempt to measure wall stress. Instead we measured the increase in end systolic pressure as an index of individual increases in afterload.²⁴ The pressure at end ejection rather than at end systole is used for the non-invasive assessment of pressure at end systole.^{12,14,25} Because both can differ considerably when there is mitral regurgitation,²⁶ and because the non-invasive measurement of the end systolic left ventricular pressure depends on the absence of an outflow tract obstruction, we studied only patients with hypertrophic non-obstructive cardiomyopathy without mitral

regurgitation. Also it has been shown that use of angiotensin II to increase the afterload abolishes both outflow tract obstruction and mitral regurgitation in hypertrophic cardiomyopathy,²⁷ thus it seems unlikely that outflow tract obstruction or mitral regurgitation developed during the increase in afterload.

In most patients with hypertrophic cardiomyopathy diastolic function is significantly impaired.¹⁻³ Early diastolic dysfunction has been extensively evaluated by digitised echocardiography.²³ Our data confirm these findings, because in our patients we found that the time between minimal cavity dimension and mitral valve opening was prolonged at baseline conditions (figs 1 and 3), indicating delayed mitral valve opening.^{23,16} The change of dimension between minimal dimension and mitral valve opening was increased, indicating incoordinate relaxation.^{2,16,17} Peak filling rate, time of rapid diastolic filling, and the contribution of rapid diastolic filling to total diastolic filling were reduced at baseline conditions in our patients (figs 1-3, table 2). This impairment of early diastolic function is probably caused by prolonged or incomplete relaxation and the reduced distensibility of the hypertrophied left ventricle.

Recently, Brutsaert *et al*^{7,8} showed that relaxation was significantly dependent on afterload. Based on this concept of "triple control of relaxation"⁸ impaired early diastolic function in hypertrophic cardiomyopathy could be partly the result of altered systolic and diastolic loading conditions. Various loading conditions, such as end systolic wall stress, wall stress after mitral valve opening, and coronary filling during isovolumic relaxation, may be altered in hypertrophic cardiomyopathy.⁸ To evaluate the load dependence of early diastolic function in hypertrophic cardiomyopathy we measured the effects of increasing afterload on early diastolic function.

We found that the indices of early diastolic function tended to become more normal when afterload was increased in patients with hypertrophic non-obstructive cardiomyopathy (tables 2 and 3, figs 1 and 3)—the time interval between minimal cavity dimension and mitral valve opening shortened, the change of dimension during this period decreased, and the time of rapid diastolic filling and the change of dimension during rapid filling increased. This improvement of early diastolic function may result in part from an increase in filling pressures during the infusion of angiotensin II. In controls we found that end diastolic dimension, and hence end diastolic fibre stretch, did not increase when afterload was increased by the infusion of angiotensin II.²⁸ This result contrasts with other agents (such as methoxamine) that are used to produce diagnostic increases in afterload.¹²⁻¹⁴

Despite improved early diastolic function the end diastolic dimension and thus overall diastolic filling did not increase with increasing afterload in patients with hypertrophic cardiomyopathy. Although the underlying mechanism(s) cannot be assessed precisely by non-invasive techniques, this effect might to some extent be the result of reduced elastic recoil, since systolic emptying deteriorated significantly with increasing afterload (figs 1 and 2).

We conclude that impaired early diastolic function in hypertrophic cardiomyopathy is at least to some extent the result of reduced afterload and that an increase in afterload does not result in normal diastolic function.

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Familial neurofibromatosis and hypertrophic cardiomyopathy

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SUMMARY Two siblings from a family in which neurofibromatosis was inherited as an autosomal dominant had hypertrophic cardiomyopathy and neurofibromatosis. Idiopathic hypertrophic cardiomyopathy may have occurred by chance in two first degree relatives with neurofibromatosis. An alternative explanation is that these diseases are both manifestations of a common hereditary defect of neural crest tissue. Another possibility is that abnormalities of catecholamine metabolism and nerve growth factor in neurofibromatosis can cause secondary ventricular hypertrophy with septal involvement.

The aetiology of hypertrophic cardiomyopathy is unknown, although genetic factors are almost certainly involved. In addition, there is increasing evidence, both clinical and experimental, of an abnormality of catecholamine metabolism. Reports of abnormal catecholamine metabolism in neurofibromatosis have led to the suggestion that there is an aetiological link between the two diseases.

Case reports

CASE 1

The index case (II.2, age 42) presented with exertional chest pain and a systolic murmur (figs 1 and 2a). There was a past history of peptic ulceration. The resting electrocardiogram showed considerable left ventricular hypertrophy. Cross sectional and M mode echocardiography (fig 2b and c) showed hypertrophic cardiomyopathy with asymmetric septal hypertrophy. The interventricular septum was 2.8 cm thick, and the posterior left ventricular wall was 1.2 cm thick. In systole there was pronounced anterior motion of the mitral valve and obliteration of the left ventricular cavity. Cardiac catheterisation and angiography showed normal coronary arteries, and a left ventricular outflow gradient of 70 mm Hg. Radionuclide ventriculography showed an ejection

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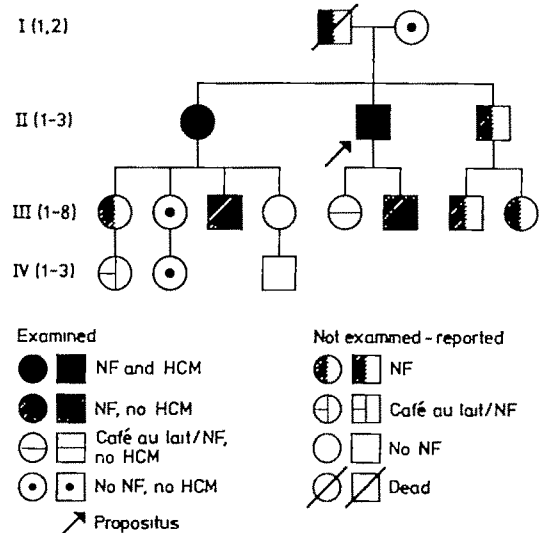


Fig 1 The family pedigree.

I.1 Father of propositus, known to have NF, died aged 64 of carcinoma of stomach; I.2 mother of propositus, alive and well, aged 74, no clinical evidence of NF or HCM; II.1 sister of propositus, aged 49, classic NF and HCM; II.2 propositus, classic NF and HCM, aged 47; II.3 brother of propositus, known to have NF, aged 46, refused examination; III.1 woman aged 26, known to have NF, refused examination; III.2 woman aged 25, examined—normal; III.3 man aged 19, classic NF, heart normal; III.4 woman aged 24, reported normal, refused examination; III.5 girl aged 5, NF of typical café au lait type, heart normal; III.6 boy aged 4, classic NF, heart normal; III.7 boy aged 9, reported NF, parents refused permission for examination; III.8 girl aged 6, reported NF (as III.7); IV.1 girl aged 7, reported NF of typical café au lait type (as III.7); IV.2 girl aged 4, normal at examination; IV.3 boy aged 3, reported normal, refused examination. NF, neurofibromatosis; HCM, hypertrophic cardiomyopathy.

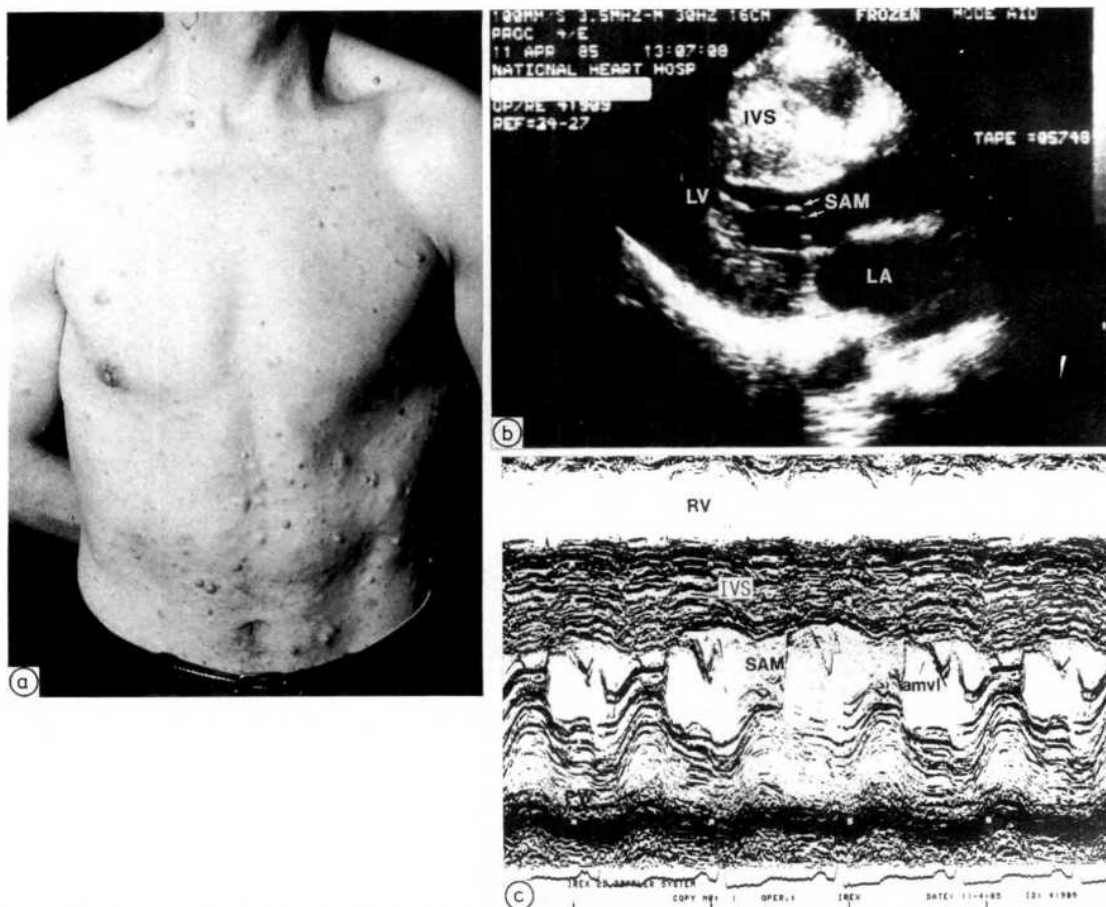


Fig 2 (a) Anterior view of chest in propositus showing multiple cutaneous neurofibromas. (b) Long axis, parasternal, cross sectional echocardiogram of propositus showing gross septal hypertrophy with typical echogenic appearance of the septal myocardium. IVS, interventricular septum; LA, left atrium; LV, left ventricle; SAM, systolic anterior motion of the mitral valve. (c) M mode echocardiographic recording showing gross thickening of the interventricular septum (IVS) and SAM. amv, anterior mitral valve leaflet; PW, posterior wall of left ventricle.

fraction of 100%, and typical features of hypertrophic cardiomyopathy. Biopsy of the skin nodules confirmed neurofibromatosis. Concentrations of plasma catecholamines and urinary catecholamine metabolites were normal. Serum concentrations of calcium and fasting gastrin were also normal.

CASE 2

The 46 year old sister of case 1 has severe kyphoscoliosis, large numbers of neurofibromas, and giant café au lait patches (fig 3a and b). Cardiovascular examination and resting electrocardiography were normal but the chest x ray showed a right paravertebral neurofibroma. Her thoracic deformity hampered echocardiography but an apical four chamber cross sectional view showed evidence of hypertrophic

cardiomyopathy (fig 3d and e) with subaortic septal hypertrophy. Cardiac catheterisation and angiography showed normal coronary arteries with a grossly abnormal left ventriculogram. There was a "ballerina foot" deformity with mid-cavity obliteration and an ejection fraction of 70%. No intracavity gradient was found. Left and right heart pressures were normal. Concentrations of plasma catecholamines and urinary metabolites were normal.

THE FAMILY

The family consisted of the index case (II.2), six first degree, and nine second degree relatives. With the exception of the index case and his sister all those examined had normal hearts. Four first degree and

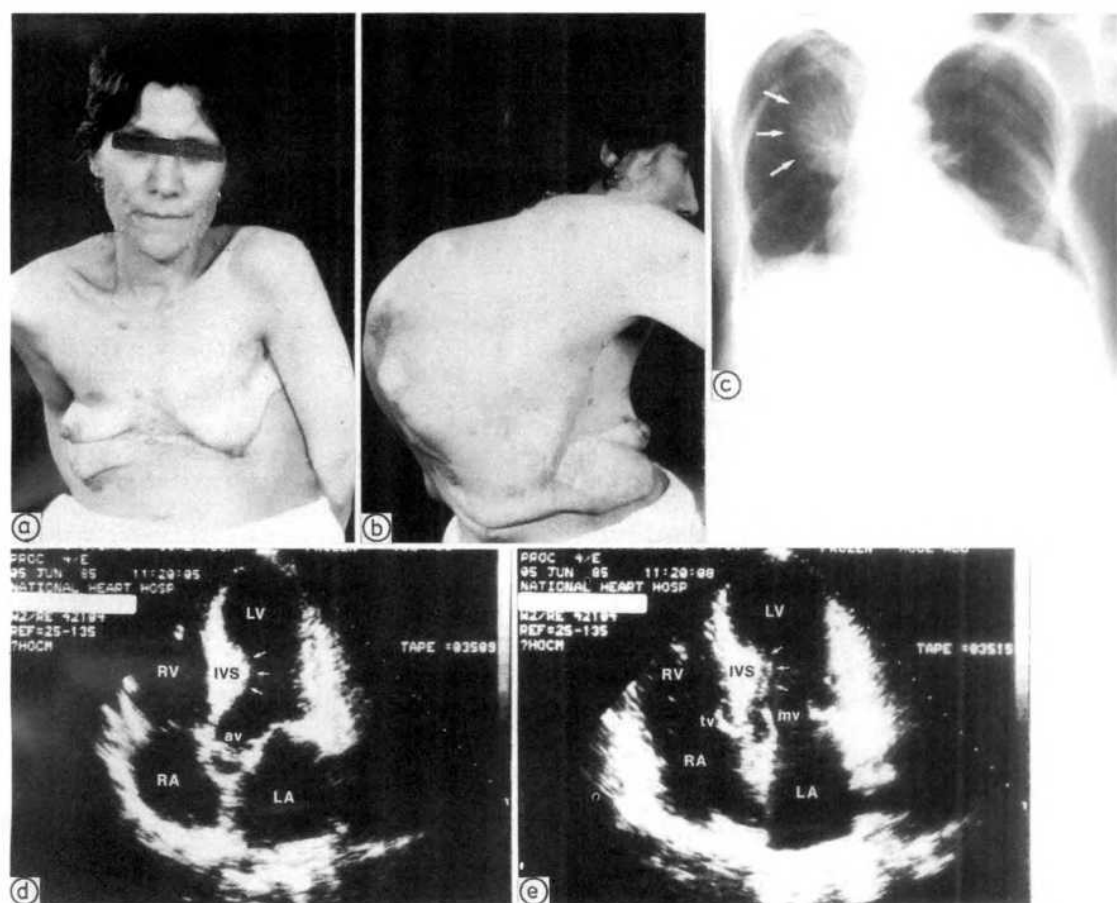


Fig 3 (a) Anterior view of case II showing typical cutaneous neurofibromas. (b) Lateral view of case II showing the severe degree of kyphoscoliosis. (c) Posterior anterior chest radiograph of case II showing the severity of her skeletal deformity and a large neurofibroma in the right upper zone (arrows). (d) Apical five chamber cross sectional echocardiogram from case II showing pronounced subaortic hypertrophy of the septal myocardium (arrows). (e) Apical four chamber view in case II showing a pronounced septal bulge above the mitral valve. av, aortic valve; IVS, interventricular septum; LA, left atrium; LV, left ventricle; mv, mitral valve; RA, right atrium; RV, right ventricle; tv, tricuspid valve.

five second degree relatives had neurofibromatosis (see fig 1).

Discussion

Cross sectional echocardiography showed hypertrophic cardiomyopathy in the index case (II.2, fig 2b) and his sister (II.1, fig 3d and e). Both had considerable asymmetric hypertrophy of the interventricular septum. There was evidence of obstruction of the left ventricular outflow tract in case II.2 which was confirmed at catheterisation, but this feature was not present in his sister (II.1). Neurofibromatosis has been misdiagnosed as lentiginosis.¹ Our diagnoses were confirmed by biopsy of the skin nodules in case

II.2 and by associated skeletal and dermatological findings in his sister (II.1).

Where neurofibromatosis is suspected in the absence of skin nodules, the diagnosis may be made by the finding of six or more café au lait skin patches of $>1.5 \text{ cm}^2$.² Neurofibromatosis was diagnosed in this way in cases III.5 and IV.1.

The association between hypertrophic cardiomyopathy and neurofibromatosis has already been reported.^{3,4} The cells responsible for the neurofibromas are of neural crest origin and it may be relevant that other neuro-ectodermal conditions have been reported in association with hypertrophic cardiomyopathy. The best known of these is lentiginosis,⁵ where the melanocytes responsible for the

skin lesions arise from the neural crest. Two studies have indicated that the association of hypertrophic cardiomyopathy and lentiginosis might be familial and autosomal dominant,^{6,7} but other family studies have failed to confirm this.⁸ Hypertrophic cardiomyopathy has been described with pheochromocytoma⁹ and parathyroid tumours.¹⁰ Symons *et al* have studied this association. They showed that patients with hypercalcaemia caused by hyperparathyroidism may have asymmetric septal hypertrophy, and also that normocalcaemic patients with hypertrophic cardiomyopathy have raised concentrations of parathyroid hormone.¹⁰ They also showed that unexplained hypertrophy may also be found in thyrotoxicosis where sympathetic activity is increased.¹¹ Tumours of the parathyroid, adrenal medulla, and medullary cells of the thyroid (all of neuro-ectodermal origin), occur together in the multiple endocrine adenoma syndrome type II, or Sipple's syndrome. This is often autosomal dominant¹² and has been reported in association with hypertrophic cardiomyopathy and with neurofibromatosis. Riccardi reported raised concentrations of catecholamines in neurofibromatosis. In at least two cases no pheochromocytoma could be found and neurofibromas were thought to be the source.¹³

There is increasing debate about the role of catecholamines in hypertrophic cardiomyopathy. Dense sympathetic innervation and high tissue catecholamine concentrations in the septal myocardium have been reported.¹⁴ Others have refuted this.^{15,16} The developing myocardium is known to be very sensitive to catecholamines, and in normal neonates circulating concentrations are already high. Experimental work by Olsen *et al* has shed some light on possible interactions in the developing myocardium. The administration of TRIAC (diethanolamine salt of triiodothyronine), a triiodothyronine analogue, to pregnant rats produced widespread cellular disarray resembling that seen in hypertrophic cardiomyopathy. This reaction could be blocked by propranolol.¹⁷ Perloff suggested that a possible mechanism for the development of hypertrophic cardiomyopathy is that catecholamine abnormalities lead to cellular disarray. He postulated that the inherent isometric contraction of malignant cells is less effective and leads to secondary myocardial hypertrophy.¹⁸ If Perloff's theory is correct myocardial disarray with subsequent hypertrophy could be a secondary phenomenon in neurofibromatosis if catecholamine concentrations are abnormal during early development when the septum is known to be hypersensitive.

Other hormonal mechanisms may be involved. Nerve growth factor is a naturally occurring

glycoprotein required for growth and maintenance of sympathetic and sensory neurones.¹⁹ Abnormal metabolism of this substance is thought to be a factor in the pathogenesis of neurofibromatosis and different forms of the disease are distinguishable by the circulating concentrations of nerve growth factor.²⁰ Whereas sensory ganglia respond only during embryogenesis, when the influence of nerve growth factor is greatest, mature sympathetic neurones remain responsive to this factor.¹⁹ Imbalance of the delicate interaction between developing myocardium, sympathetic innervation, catecholamines, and nerve growth factor has been proposed as a model for the pathogenesis of hypertrophic cardiomyopathy.¹⁸

We found hypertrophic cardiomyopathy and neurofibromatosis in two siblings. There are three possible explanations for this. Firstly, the two diseases could have appeared together by chance, although this seems unlikely. Both are relatively common conditions with a similar incidence, about 1:3000,^{13,21} although this figure is less certain in the case of hypertrophic cardiomyopathy.²² Secondly, left ventricular hypertrophy may be secondary to neurofibromatosis, perhaps as a result of abnormal metabolism of catecholamines or nerve growth factor. Thirdly, both diseases could be common manifestations of a defect of neural crest tissue with autosomal dominant inheritance.

The known coincidence of hypertrophic cardiomyopathy with conditions such as lentiginosis and hyperparathyroidism argues in favour of a common defect of the neural crest. This seems more plausible than secondary left ventricular hypertrophy in the presence of an abnormality of catecholamines or nerve growth factor, which may occur in neurofibromatosis. Furthermore, neurofibromatosis is independently associated with hyperparathyroidism and with Sipple's syndrome,¹³ and the pattern of asymmetric septal hypertrophy seen in these two cases is indistinguishable from that seen in idiopathic hypertrophic cardiomyopathy.

There is circumstantial evidence suggesting a link between neurofibromatosis and hypertrophic cardiomyopathy. Abnormalities of catecholamine metabolism, sympathetic innervation, and nerve growth factor may account for the development of idiopathic left ventricular hypertrophy in certain subjects with neurofibromatosis. An alternative explanation, supported by the known association of both conditions with other diseases of neural crest origin, is that they are genetically linked. The sequence containing the gene for neurofibromatosis has recently been located by linkage analysis to polymorphic markers on chromosome 17.²³ We speculate that this could lead to the identification of a genetic marker for hypertrophic cardiomyopathy.

We thank Caroline Westgate for the echocardiography.

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Demonstration of the ascending aorta in infective endocarditis by intravenous digital subtraction angiography

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SUMMARY Four patients with infective endocarditis were examined by digital subtraction angiography immediately before operation. In three a root abscess was suspected and the remaining patient was believed to have a false aneurysm at an infected aortic cannulation site. In all the cases digital subtraction angiography showed the structure in several projections and confirmed the presence of a cavity. Subsequent operation confirmed the site and nature of the lesions.

Endocarditis of a native cardiac valve develops in about 16 patients per million population per year in the United Kingdom. The overall mortality is 35%. After the exclusion of patients who die before treatment can be started, the mortality in adequately treated patients is 24%.¹ The overall cumulative risk of developing either early or late infective endocarditis after the insertion of a prosthetic heart valve is about 5%.^{2,3} About 75% of patients with this complication die if medical treatment alone is used. Mortality falls to approximately 50% if operation and valve replacement are performed promptly.^{4,5} Medical treatment is much less likely to be successful if the infection has spread through the aortic wall to produce abscess cavities or false aneurysms, which like aneurysms increase in size. This increases the risk of operation, but this treatment offers the best prospect of cure. First degree heart block in these patients suggests the presence of a septal abscess⁶⁻⁸ but is not a sufficiently definitive sign to prompt a change from medical to surgical treatment at an unpropitious time. The objective demonstration of a root abscess is important^{9,10} and it has been attempted by arterial arteriography, echocardiography, and computed tomography. Root aortography gives the best evidence¹¹ but this procedure can displace friable infected material from the valve or abscess cavity and requires arterial puncture. The suitability of

computed tomography has not yet been established for this purpose. Echocardiography is a valuable screening tool but may give an equivocal picture in many cases.¹²⁻¹⁴

Intravenous digital subtraction angiography does not require intra-aortic injection of contrast. It gives good quality images of the aortic root and any abnormal cavities, and it can be used even in ill patients.

Patients and methods

Four patients with infective endocarditis were studied within a period of 20 months. In three patients there were electrocardiographic changes suggestive of abscess formation in the aortic root or interventricular septum. One had native valve endocarditis and two had prosthetic valve endocarditis. The fourth patient had widening of the mediastinum after replacement of the aortic valve and an infected cannulation site on the ascending



Fig 1 Electrocardiograms showing a normal PR interval before infective endocarditis developed in patient 1.

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Fig 2 Electrocardiograms showing a prolonged PR interval in patient 1 taken after infective endocarditis developed.

aorta was suspected. Intravenous digital subtraction angiography was performed to show the structure and confirm the presence of a cavity. Cardiac images were obtained with the Technicare DR 960 digital subtraction angiography unit. Data were acquired at a frame rate of between 2.5 and 5 frames/s with a 12 pulse three phase smoothed generator. Pixel resolution was between 0.3 and 0.6 mm. The equipment and techniques are described in detail elsewhere.^{15,16} In this series, a 5 French gauge straight catheter with multiple side holes was inserted into the superior vena cava or right atrium by means of a percutaneous modified Seldinger approach through the median cubital vein of the right arm. Data were acquired in the left anterior oblique and in the right anterior oblique orientation. A bolus of 40 ml of non-ionic contrast material was injected at 25 ml/s and images were obtained over the region of interest. The size of the image intensifier (22 cm) allowed most of the aortic arch to be included in the field of view. Patients were asked not to breathe during the acquisition of

the image series. Diagnostic images were obtained in all cases, though some image processing was necessary to obtain the best combination of mask and data images to produce the optimal subtraction image.

CASE REPORTS

Case 1

A 58 year old man presented with a one week history of malaise, fever, and rigors seven months after he had undergone aortic valve replacement for tight aortic stenosis. A new early diastolic murmur was present at the left sternal edge. Infective endocarditis was confirmed by a blood culture which grew *Staphylococcus epidermidis*. Treatment with benzylpenicillin and gentamicin was started. A previous electrocardiogram showed a normal PR interval (fig 1). But on this admission the electrocardiogram showed first degree heart block, suggesting the presence of an aortic root or septal abscess (fig 2). The intravenous digital subtraction angiogram showed a large anterior aortic root cavity (fig 3). Additional cavities were excluded by a review of the digital subtraction cine sequence. Subsequently the patient underwent operation to eliminate this focus of infection. During the operation we confirmed that the site and nature of the abscess accorded with the digital subtraction angiogram; a photograph taken at operation shows the extent of the cavity (fig 4).

Case 2

A febrile illness developed in a 56 year old man

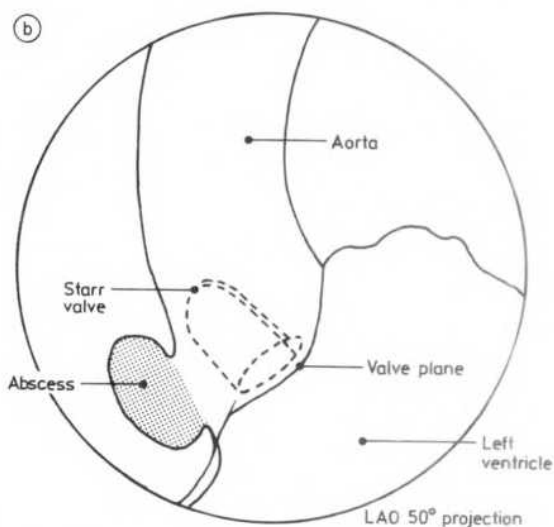
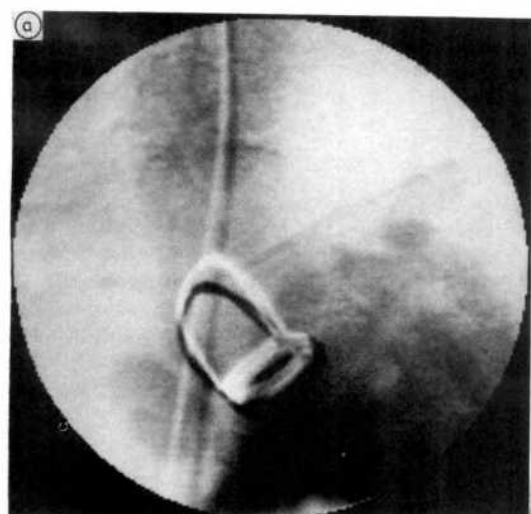


Fig 3 (a) and (b) Single subtraction frame from the intravenous digital subtraction angiogram in patient 1 showing the extent of the aortic root abscess.

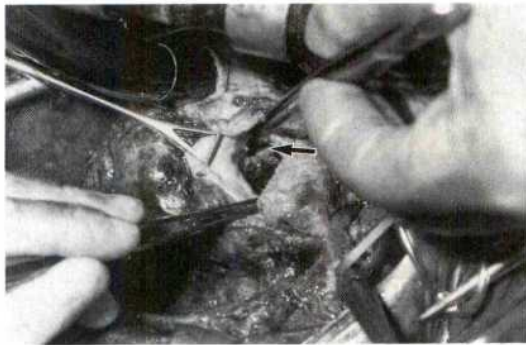


Fig 4 A peroperative photograph in patient 1 showing the origin of the paravalvular cavity (arrowed).

during convalescence after aortic valve replacement for tight aortic stenosis. A chest radiograph at the time showed a wide mediastinum (fig 5) and computed tomography of the chest was performed. An abnormal anterior mediastinal shadow was present, and injection of contrast showed that this was vascular (fig 6). Sagittal and coronal reconstruction of the computed tomographic scan showed an aneurysm of the ascending aorta (fig 7) but failed to provide adequate anatomical detail. An intravenous digital subtraction angiogram was performed and showed an abscess cavity adjacent to the ascending aorta (fig 8). This false aneurysm displaced the innominate artery and part of the anterior wall of the

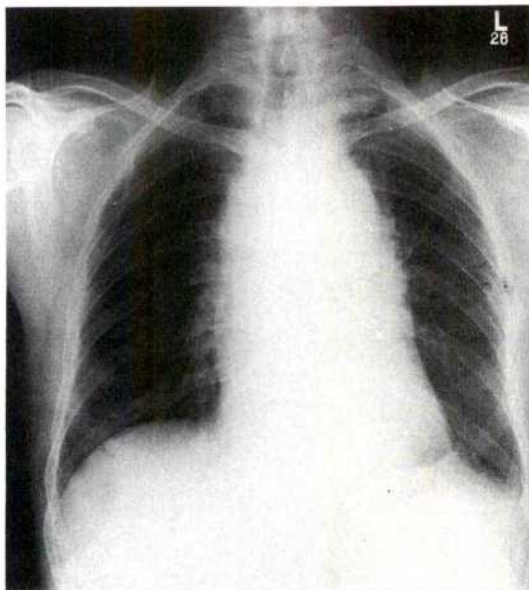


Fig 5 Chest radiograph in patient 2 showing widening of the mediastinum at the level of the aortic arch.

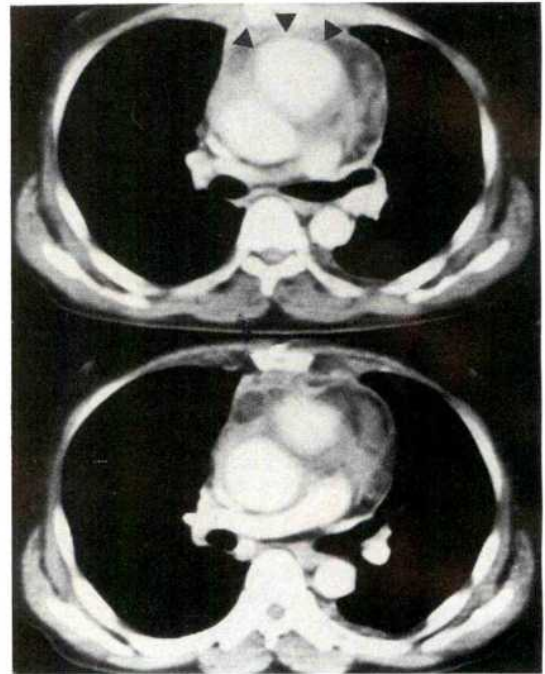


Fig 6 Computed tomograms of two adjacent axial sections of the mediastinum in patient 2 after contrast injection showing an abnormal collection (arrowed) in the anterior mediastinum displacing the aortic arch.

aorta just proximal to the origin of the innominate artery. The digital subtraction image (fig 8c) gave a clearer indication of a narrow neck than the computed tomographic image. Both techniques showed the site and size of the cavity. At operation an infected false aneurysm with a narrow neck was resected and the aorta was patched. Cultures of resected tissue grew *Staphylococcus aureus*.

Case 3

A 29 year old woman who had aortic valvotomy at the age of 12 was admitted with a history consistent with infective endocarditis. Blood cultures grew *Staphylococcus sanguis*. Treatment with benzylpenicillin was started. Serial electrocardiograms showed prolongation of the PR interval, and an aortic root abscess was suspected. Intravenous digital subtraction angiography showed a large cavity in the para-aortic region, close to the aortic valve ring (fig 9). Operation confirmed the site and extent of the cavity.

Case 4

A 60 year old man, who had undergone replacement of a calcified bicuspid aortic valve, presented six

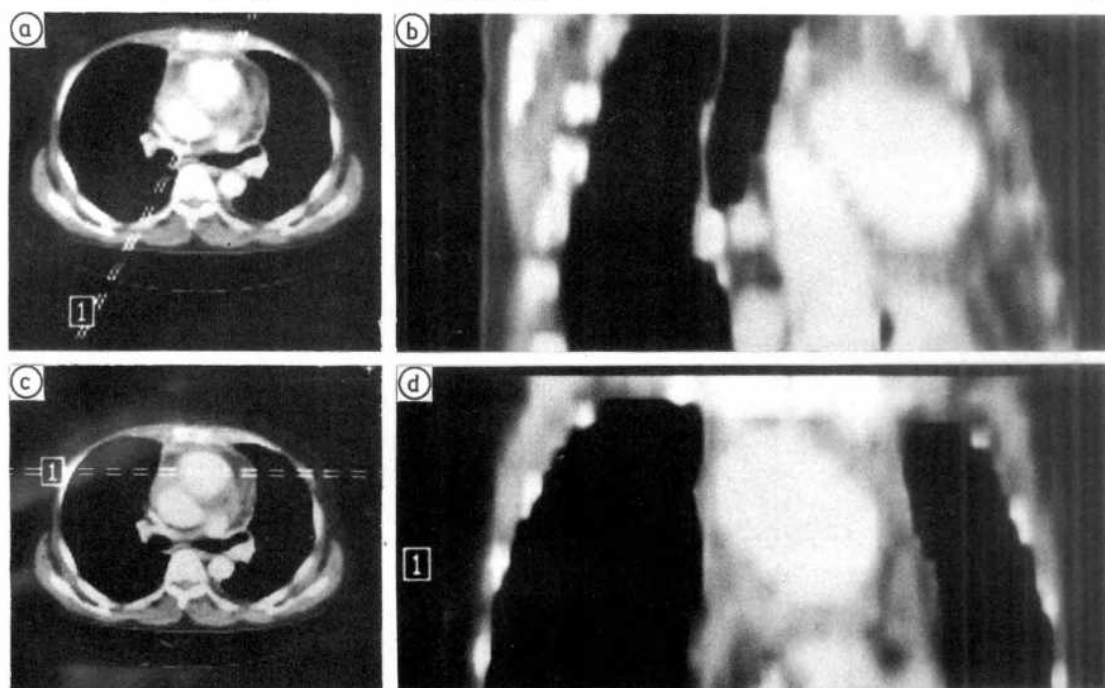


Fig 7 (b and d) Computer controlled reconstructions of the axial scans in fig 6. Dashed lines (a and c) indicate the oblique plane of the reconstruction and the coronal plane of the reconstruction.

months later with fever and rigors after dental treatment covered with amoxycillin. Infective endocarditis was confirmed by the growth in blood cultures of a micrococcus that was resistant to penicillin. Treatment was started with gentamicin and teicoplanin. The electrocardiogram at that time showed new first degree heart block, and an intravenous digital subtraction angiogram was performed which showed a small anterior aortic root cavity (fig 10) above the sinuses of Valsalva. The development of first degree heart block was probably caused by the formation of micro-abscesses within the intraventricular septum. At operation the valve was replaced and the aortic root was repaired.

Discussion

These four patients were the only patients seen in our unit in 20 months with aortic valve endocarditis who were thought to have an aortic root abscess on clinical grounds (long PR interval in 1, 3, and 4, and chest x ray in case 2). This small series cannot test the diagnostic accuracy of intravenous digital subtraction angiography of the aortic root, but an abscess cavity was demonstrated in all patients in whom it was clinically suspected.

The high mortality associated with complicated infective endocarditis may be reduced by prompt operation and replacement of the aortic valve (either native or prosthetic). Criteria for operation include (a) refractory heart failure caused by valvar regurgitation, (b) uncontrollable infection, (c) an increasing PR interval, and (d) septic embolism. In patients in whom the PR interval has increased and an abscess cavity is suspected preoperative confirmation is useful. Echocardiography is the least invasive of the available options but it does not always produce useful images. It is not always possible to get good images of the aortic root on echocardiography, and results may be equivocal.¹²⁻¹⁴ In one of our patients computed tomography scanning was an early investigation; despite reasonably good reconstructions the origin of the abscess was not demonstrated adequately, and in general the best resolution available with this technique is in the order of 4 to 5 mm. Because of this low resolution it is not the best investigation to show the features of the ascending aorta.

Digital subtraction angiography, even in very ill patients, can provide images of sufficient quality to be useful in confirming the site and size of a suspected abscess cavity. In the patients we studied, the extent

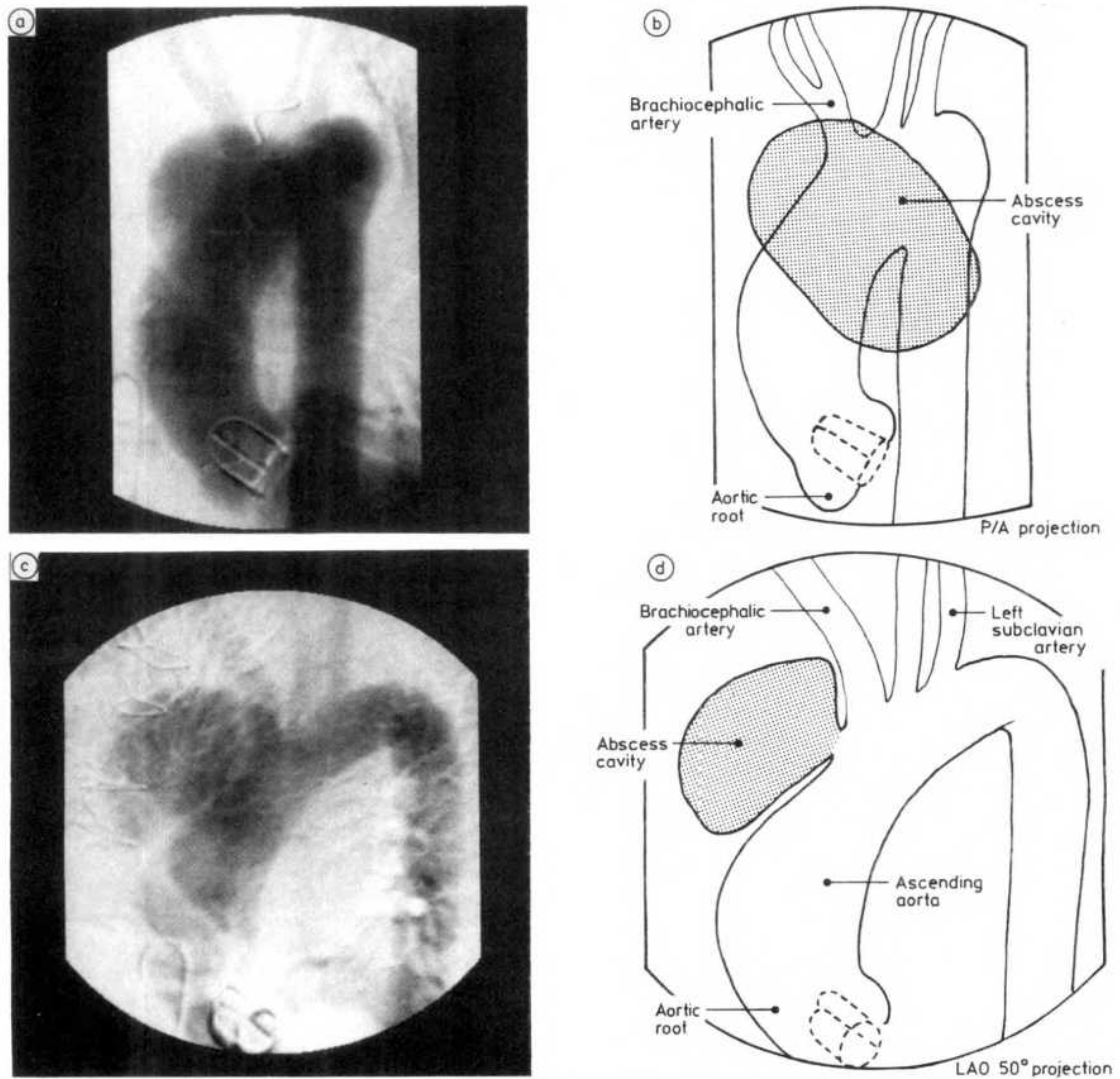


Fig 8 Intravenous digital subtraction angiogram of patient 2 showing aortic root abscess cavity in posteroanterior projection (a and b) and left anterior oblique projection (c and d). The abscess cavity was an infected false aneurysm just proximal to the origin of the innominate artery.

of the abscess was shown, as well as the size of its origin and track. In patient 4 the digital subtraction image showed a cavity well above the sinuses of Valsalva and the first degree heart block was probably the result of micro-abscess formation within the intraventricular septum. True intraseptal cavities would be missed by this technique. None of the patients needed an arterial study before operation, so the potential complications of direct injection of contrast into the aorta were avoided. Some post-

processing of the image series is almost always necessary to obtain a combination of mask and data image that reduces the movement artefact in the region of interest to negligible proportions. The facility to choose the mask and data images independently of each other is a feature of the second generation of digital subtraction angiographic equipment. It is an essential part of producing diagnostic studies. Each of the images shown is a single frame from a digital subtraction cine sequence and much

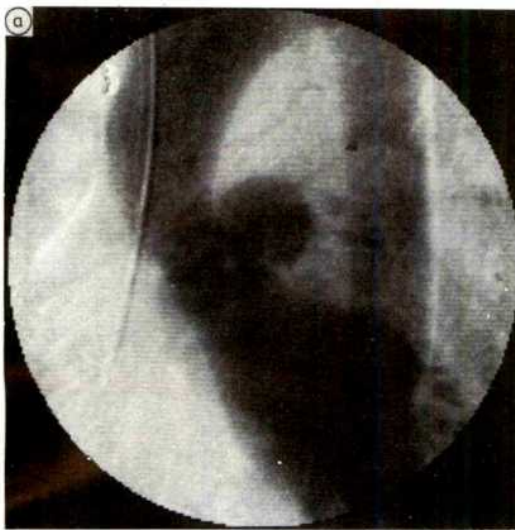
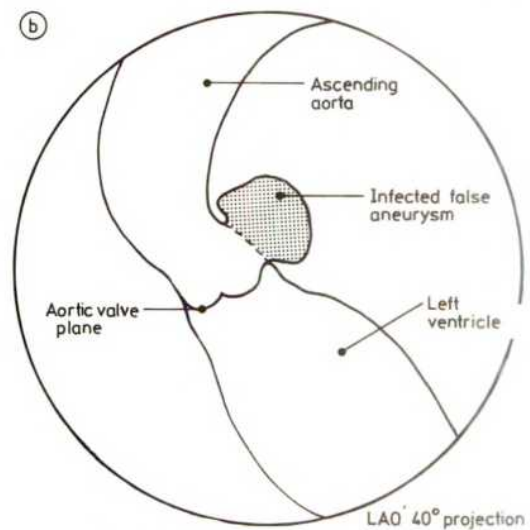


Fig 9 Intravenous digital subtraction angiogram of patient showing aortic root and infected false aneurysm in the 40° left anterior oblique projection.



more information can be obtained from examination of the whole sequence rather than from a single frame.

Intravenous digital subtraction angiography gives high quality images of the ascending aorta in patients with suspected abscess formation without the need for arterial catheterisation. Such images may be sufficient to plan subsequent operation and avoid the

possible complications of direct aortic root catheterisation and injection of contrast.

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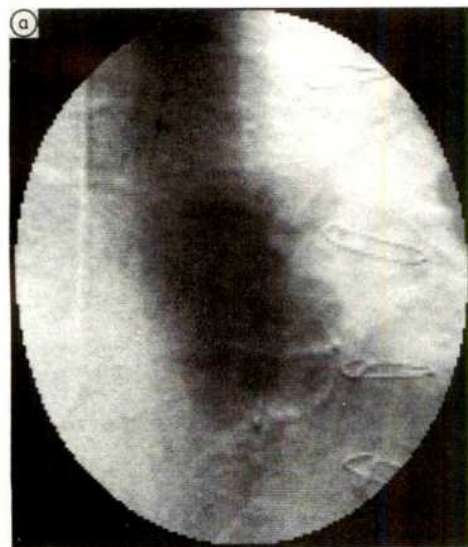
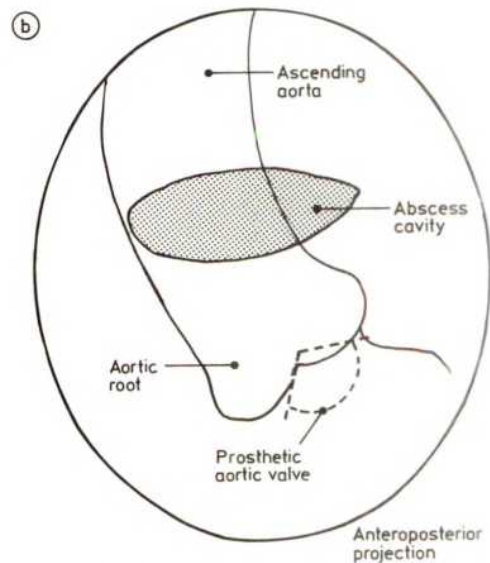


Fig 10 Intravenous digital subtraction angiogram of patient 4 showing aortic root and abscess cavity in the posteroanterior projection.



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Case reports

Imperforate tricuspid valve with single cardiac outlet from right ventricle

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SUMMARY A cyanosed neonate was diagnosed as having concordant atrioventricular connection and single cardiac outlet and aorta from right ventricle with atresia of the pulmonary valve. She underwent a systemic to pulmonary artery shunt and is now thriving. Additionally, the tricuspid valve was imperforate and a large ventricular septal defect caused an unusual pattern of intracardiac blood flow. The tricuspid valve ring and right ventricular cavity appeared to be of normal size. The good outcome in this patient suggests that these features may be advantageous for corrective operation.

Two different forms of tricuspid atresia have been reported.¹ These are a univentricular atrioventricular connection with absence of the right atrioventricular ostium (classic "tricuspid atresia") and a biventricular atrioventricular connection with an imperforate tricuspid valve. The latter is much less frequent and is usually associated with right ventricular hypoplasia. The abnormal ventriculoarterial connection in the present case resulted in a convoluted blood flow pattern and was associated with an unusually well developed tricuspid valve annulus and right ventricle.

Case report

A 4.2 kg full term female infant was centrally cyanosed from 12 hours of age. Abnormal findings were a single second heart sound and a 2/6 ejection systolic murmur at the left sternal edge. No separate ductal murmur was audible despite an infusion of prostaglandin E₂. Arterial Po₂ was 3.8 kPa in air and 6.8 kPa in 100% oxygen. The electrocardiogram showed sinus rhythm with normal P waves, a QRS axis of +20° and left ventricular dominance, and the

chest radiograph showed reduced perfusion of the lungs.

Cross sectional echocardiography showed normal arrangement of the abdominal great vessels, normal venous return, concordant atrioventricular connection, and probable double outlet right ventricle, with the large aorta arising anterior and to the right of the atretic pulmonary valve and small pulmonary trunk. The branch pulmonary arteries were small. A left aortic arch and large arterial duct were present. The right ventricle was of normal size and communicated with the left ventricle via a large perimembranous ventricular septal defect (fig 1a). A muscular defect was also seen. A mobile but imperforate membrane was seen between the right atrium and ventricle. There was at least one chordal attachment from the ventricular surface of the valve to the interventricular septum (fig 1b). Doppler echocardiography did not detect flow across the valve. The pattern of interatrial flow was readily appreciated by visualisation of the margins of the foramen ovale which opened widely into the left atrium during each diastole and showed a biphasic leftward movement that mirrored the movement of the mitral valve.

A right modified Blalock shunt was constructed with a 4 mm diameter polytetrafluoroethylene tube.

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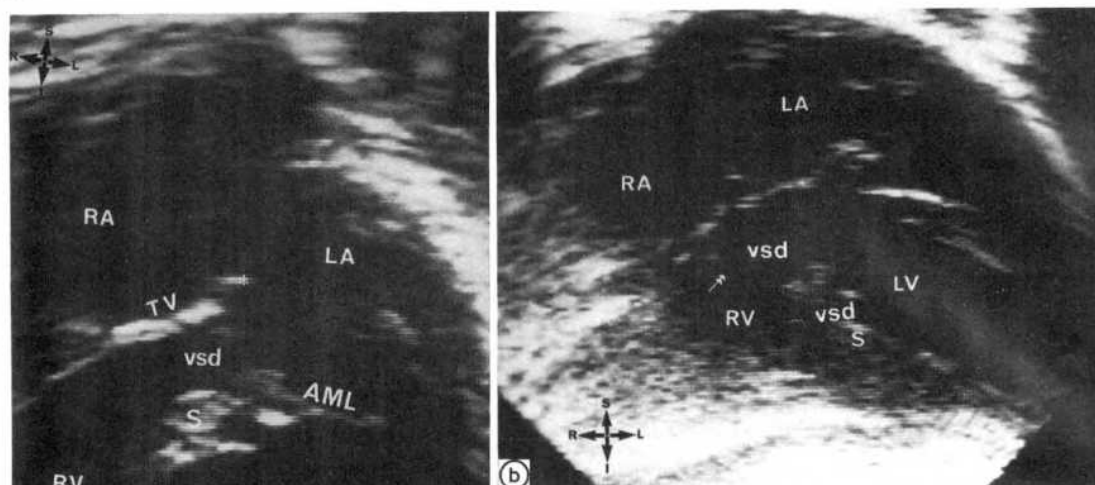


Fig 1 Cross sectional echocardiograms. (a) Parasternal four chamber view in diastole showing imperforate tricuspid valve (TV) separating the right atrium (RA) and right ventricle (RV). The anterior leaflet of the mitral valve (AML) is open and the septum secundum (*) has bowed into the left atrium (LA). The perimembranous inlet ventricular septal defect (vsd) is visible between the interventricular septum (S) and the conjoined atrioventricular valves. (b) Subcostal view in systole showing large inlet and smaller muscular ventricular septal defects (vsd), closed mitral valve, and imperforate tricuspid valve with tensor apparatus (double-headed arrow).

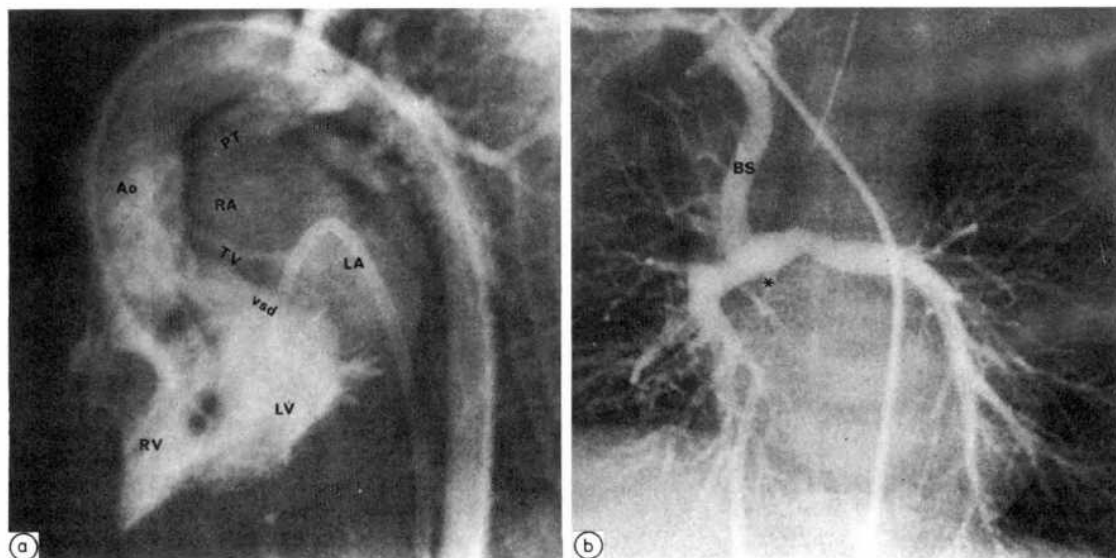


Fig 2 (a) Left ventriculogram in a four chamber projection showing the large inlet ventricular septal defect (VSD) and normal sized right ventricle (RV). Mitral regurgitation induced by extra systoles resulted in contrast washing back via the left atrium (LA) into the right atrium (RA). The imperforate tricuspid valve (TV) is clearly profiled between the right atrium and ventricle. The aorta (Ao) arises from the right ventricle. The narrow, blind-ending pulmonary trunk (PT) filled retrogradely via the shunt. LV, left ventricle. (b) A subclavian arteriogram showing filling of the modified Blalock shunt (BS), the right and left pulmonary arteries, and the blind-ending, right sided pulmonary trunk (*).

Her colour improved but she remained mildly tachypnoeic. Cardiac catheterisation was therefore performed at the age of seven weeks. The mean right and left atrial pressures were 5 and 4 mm Hg respectively. Simultaneously measured left ventricular and ascending aortic systolic pressures were equal. There was an atrial right to left shunt with equal left atrial and aortic oxygen saturations (82%). When contrast was injected into the right atrium it passed without hold-up into the left atrium and then into the left ventricle, right ventricle, ascending aorta, and finally via the patent shunt into the pulmonary arteries. The same injection also showed left juxtaposition of the atrial appendages. Left ventriculography (fig 2a) showed the perimembranous ventricular septal defect and confirmed that there was no arterial outlet from this chamber. Extrasystoles induced mitral regurgitation which resulted in reflux of contrast into the left atrium and then the right atrium. The imperforate tricuspid valve was thus outlined between the right atrium and ventricle. An injection of contrast into the shunt showed equal filling of rather small pulmonary arteries and outlined the small blind-ending pulmonary trunk (fig 2b). Pulmonary venous return was normal. Thus no further surgical intervention was required. Her breathing and weight gain are now normal.

Discussion

In classic tricuspid atresia the right atrioventricular connection is absent and this entity is far more frequent than an imperforate tricuspid valve.¹ An imperforate tricuspid valve must be distinguished from the imperforate form of Ebstein's anomaly² and from the imperforate right side of a common valve in complete atrioventricular septal defect.³ All are rare. As in the present case, cross-sectional echocardiography facilitates the diagnosis, especially when the imperforate valve is thin and mobile and a hypoplastic tensor apparatus is seen.⁴

An imperforate tricuspid valve is always accompanied by other lesions. Usually the right ventricle and tricuspid annulus are hypoplastic and there is pulmonary stenosis or atresia with or without a small ventricular septal defect^{2,4} or absence of the pulmonary valve.⁵ Dickinson *et al* described three hearts with an imperforate tricuspid valve, ventricular septal defect, and discordant ventriculoarterial connection; but in all the inlet portion of the right ventricle was hypoplastic.⁶ In an anatomical study Wilkinson *et al* reported a single case of imperforate tricuspid valve associated with double outlet right ventricle but they gave no details.⁷

As far as we are aware the present case is the first description of an imperforate tricuspid valve and single cardiac outlet from the right ventricle. In contrast to previous cases of imperforate tricuspid valve, the tricuspid annulus and, accordingly, the inlet portion as well as the trabecular and outlet portions of the right ventricle are of normal size. These features may be related to a flow pattern resulting from lack of an arterial outlet from the left ventricle and a large ventricular septal defect. The right ventricle in this case is an indispensable link in the tortuous passage of blood from the veins to great arteries.

Surgical palliation was remarkably successful. Future corrective operation may include closure of the ventricular septal defect with incorporation of the aorta into the left ventricle, and construction of a right ventricle to pulmonary artery conduit—in addition to excision of the tricuspid valve and the placement of a tricuspid valve prosthesis.

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Pericardial obliteration by angiosarcoma

M G CHEESMAN, J WEBSTER, D ROWLANDS

From the Department of Medicine, University of Wales College of Medicine, Heath Park, Cardiff

SUMMARY Primary cardiac angiosarcoma caused pericardial obliteration and death from tamponade in a 66 year old man.

Angiosarcoma of the heart is an uncommon malignancy with a very poor prognosis. It most commonly presents as a bloodstained pericardial effusion, and fever, pericardial pain, weight loss, and night sweats are typical. Few patients survive more than a few months, partly because of delayed recognition, with tuberculosis being the commonest misdiagnosis. Echocardiography may be helpful in diagnosis, and there are a few reports of early operation and extended life span¹; however, many cases are diagnosed at necropsy. The mode of death is obscure in most cases, though in some necropsy series the pericardial space was obliterated by the tumour, and death was caused by tamponade. We report such a case.

Case report

A 66 year old white man presented with a three month history of progressive exertional dyspnoea, dry cough, and anorexia. For two weeks he had experienced profuse night sweats and aching central chest pain made somewhat worse by deep breathing but not by any postural change; he had continued to work. There was no relevant past medical or family history, and no exposure to any industrial chemicals.

On examination he was feverish (37.8°C) but looked well. He had a resting sinus tachycardia, an impalpable apex beat, and very quiet heart sounds. Jugular venous pressure extended above the angle of the jaw. Arterial blood pressure was 95 mm Hg systolic in expiration with a 20 mm Hg paradoxical wave. A posterior-anterior chest x ray showed massive globular cardiomegaly, and a cross sectional echocardiogram confirmed a very large pericardial effusion, though the heart appeared to be normal.

The effusion was tapped and 3 l of bloodstained pericardial fluid was obtained: there was an

immediate improvement in haemodynamic function. No malignant cells were obtained from the fluid, although numerous lymphocytes and some debris were seen. No acid fast bacilli were seen on smear or cultures. A Mantoux skin test was strongly positive at 1/1000. A presumptive diagnosis of tuberculosis was made and treatment was started with rifampicin, isoniazid, ethambutol, pyrazinamide, and prednisone.

He continued to lose weight and two weeks later was readmitted with lethargy and malaise. Findings were essentially unchanged except that he had lost 6 kg in weight, his jugular venous pressure was elevated by 10 cm, and the arterial paradox was 10 mm Hg. A repeat echocardiogram showed a small amount of residual effusion and material was seen to be floating in the fluid. This was thought to be fibrin and old blood. A repeat pericardiocentesis obtained only 300 ml of bloodstained fluid. No malignant cells or acid fast bacilli were seen in the fluid. There was no detectable arterial paradox after the procedure.

A computed tomogram of the thorax and upper abdomen confirmed a pericardial effusion with a normal heart (fig 1). No solid tumour was seen in the thorax. Multiple metastases were seen within the liver, however. That night the patient was found to



Fig 1 Computed tomogram of the thorax at mid-thoracic level showing the heart surrounded by pericardial tumour.

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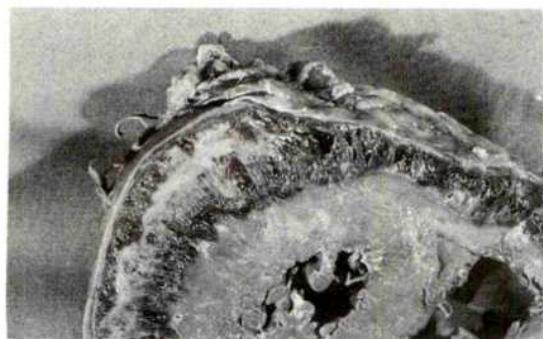


Fig 2 Pathological specimen showing the heart encircled by necrotic tumour.

be asystolic, and in view of the radiographic findings resuscitation was not attempted.

At necropsy important findings were confined to the heart and liver. The pericardial cavity was obliterated by a purple, haemorrhagic tumour infiltrating into the pericardial surface of the heart, with no clear plane of cleavage between the tumour and the heart (fig 2). The wall of the right atrium that was lateral and inferior to the opening of the superior vena cava was almost completely replaced by tumour. Multiple necrotic secondary deposits were found within the liver; no metastases were found in any other organs. Histology of the tumour showed it to be an angiosarcoma with extensive haemorrhage and necrosis.

Discussion

Primary angiosarcoma of the heart typically originates in or around the right atrium: dyspnoea may result from obstruction of the caval veins or of the right ventricular inflow and from pericardial tamponade. The fever, sweats, and high erythrocyte sedimentation rate are presumably a reaction to necrotic tumour. In contrast to hepatic angiosarcoma, there is usually no industrial exposure to environmental carcinogens. Although echocardiography may show a polypoid mass within the right atrium or pericardium, findings are not always diagnostic.

Glancy *et al* reviewed 41 cases of cardiac angio-

sarcoma at necropsy and found that in 13 the pericardial space was obliterated by tumour.² In the reviews by Janigan *et al* a similar proportion (20 of 43 cases) had pericardial obliteration by tumour,³ and in both reviews a majority presented with haemopericardium. Many patients were previously fit and presented abruptly with large effusions in pericardial tamponade. Lin *et al* also described a case like ours in which an encasing pericardial angiosarcoma gave the appearance of a pericardial effusion.⁴ Although echocardiography usually readily shows polypoid lesions within the pericardial space, we found great difficulty in differentiating between the fibrin and thrombus commonly seen in proteinaceous effusions and concentric sessile tumours. The computed tomograms in this case showed metastases but did not differentiate between pericardial fluid and tumour. Shin *et al* reported a cardiac angiosarcoma diagnosed by computed tomography, but the tumour was polypoid and clearly arose from the right atrium.⁵

Complex diagnostic aids have important limitations in the diagnosis of primary angiosarcoma of the heart if the tumour is confined in the thorax to the pericardial space and is not polypoid. Early open biopsy in persistent unexplained bloody pericardial effusion, as suggested by Strohl,⁶ may allow early diagnosis.

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Correspondence

Pulmonary atresia with ventricular septal defect and coronary artery fistula: a late presentation

Sir,

The case report by Vigneswaran and Pollock (1988;59:387-8) illustrates the continuing problems with the choice of the most appropriate words to describe congenital heart disease. They reported a patient with a solitary arterial trunk and complete absence of intrapericardial pulmonary arteries, with a connection between a coronary artery and the pulmonary arteries at the lung hilum. They described the arterial trunk as "truncus type IV". The problem with this description is that, in the absence of any intrapericardial pulmonary arteries, it is not possible to know whether initially, during development, the trunk had been an aorta or a common arterial trunk. For this reason, as suggested by Thiene and myself,¹ it might be better simply to describe the great artery as a solitary trunk.

Also, Vigneswaran and Pollock describe the communication between the pulmonary arteries and the left coronary artery as a fistula. In that the structure functions as a conduit from the heart to the lung, it certainly is a fistulous communication. Previously, however, the term "coronary pulmonary arterial fistula" was used in cases such as those described by

Rastelli (reference 3 in Vigneswaran and Pollock's case report) and subsequently described in greater detail by Krongrad *et al.*² It seems to me that the communication in the case of Vigneswaran and Pollock is more akin to a systemic-pulmonary collateral artery arising from the left coronary artery and might better be described as such.

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Spontaneous resolution of a dissection of the descending aorta after medical treatment with a β blocker and a calcium antagonist

Sir,

We read with interest the report by Hoshino *et al* (1987;58:82-4) of spontaneous resolution of a dissection of the descending aorta. The computed tomographic scans in this case illustrate some of the poorly understood aspects of the pathogenesis of aortic dissection, which should be pointed out. In fig 1, the non-opacified crescentic area alongside the narrowed aortic lumen is characteristic of intramural haemorrhage without intimal tear. The false lumen did not become opacified because there was no intimal tear. Rupture of the vasa vasorum was the likely source of haemorrhage. As the haematoma was absorbed, the aortic lumen enlarged and the crescent

disappeared. This is seen in fig 2. These observations are confirmed by a recent report of 13 cases of aortic dissection without intimal breaks, diagnosed by computed tomography and magnetic resonance imaging.¹ The diagnosis in such cases is often missed by angiography, as shown in another study of type III aortic dissections.²

Intramural haemorrhage caused by rupture of the vasa vasorum is probably the initiating event in most aortic dissections. The intimal rupture is then a secondary event responsible for propagation of dissection and further complications. In the absence of rupture, complete healing is possible as shown by Hoshino *et al*. This is particularly true for dissec-

Correspondence

tions limited to the descending aorta.^{1,2}

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This letter was shown to the authors, who reply as follows:

Sir,

We are grateful to Dr Singh and colleagues for their complimentary remarks on our case report. Their suggestion is appealing. None the less, intimal rupture was evident in our case on the 42nd day, when a contrast enhanced computed tomographic scan showed that the false lumen was opacified.

Tatsuo Hoshino, Minoru Ohmae, Akira Sakai,
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Japan.

Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 22 to 24 November 1988. The closing date for receipt of abstracts was 24 June 1988.

The Annual General Meeting for 1989 will take place in Oxford on 6 and 7 April 1989, and the closing date for receipt of abstracts will be 6 January 1989.

Embryonic origins of defective heart development

A meeting on the Embryonic Origins of Defective Heart Development will take place at the Key Bridge Marriott Hotel, Alexandria, Virginia on 4 to 6 May 1989. For further information please contact the Conference Department, The New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021, USA.

Intensive care and emergency medicine

The 9th International Symposium on Intensive Care and Emergency Medicine will take place at the Brussels Congress Centre on 21 to 24 March 1989. Inquiries to Mrs S Smits-de Smet, Erasmus University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium.

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